Major Depression - neuropsychologische und immunologische Aspekte eines heterogenen Störungsbildes

Dissertation

zur Erlangung des Doktorgrades der Naturwissenschaften

(Dr. rer. nat.)

dem Fachbereich Psychologie der Philipps-Universität Marburg

vorgelegt von

Anna Katharina Dannehl

aus Osterode im Harz

Marburg an der Lahn, März 2017

Fachbereich Psychologie
der Philipps-Universität Marburg (Hochschulkennziffer 1080)
als Dissertation am _____ angenommen.
Erstgutachter: Prof. Dr. Winfried Rief, Philipps-Universität Marburg
Zweitgutachter: Dr. Frank Euteneuer
Tag der mündlichen Prüfung (Disputation): _____

DANKSAGUNG

(Die Danksagung ist nicht Teil der Veröffentlichung).

INHALTSVERZEICHNIS

Abkürzungsverzeichnis

BDI-II	Beck Depression Inventar-II
CBASP	Cognitive Analysis System of Psychotherapy
CBT	Cognitive Behavioral Therapy
CRP	C-reaktives Protein
CTQ	Childhood Trauma Questionnaire
DSM	Diagnostic and Statistical Manual of Mental Disorders
HPA-axis	Hypothalamic-pituitary-adrenal-axis
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-10	Interleukin-10
KVT	Kognitive Verhaltenstherapie
MD	Major Depression
MKT	Metakognitive Therapie
SOMS	Screening für somatoforme Störungen
TNF-alpha	Tumor-Nekrose-Faktor-alpha
VLMT	Verbal Learning Memory Test
WHO	Weltgesundheitsorganisation

1. Zusammenfassung und Abstract

1.1. Zusammenfassung

Die Major Depression ist ein heterogenes Störungsbild, welches mit psychobiologischen und neuropsychologischen Veränderungen assoziiert ist. Die vorliegende kumulative Dissertation setzt sich aus drei Originalarbeiten zusammen, die sich inhaltlich mit verschiedenen Symptombereichen einer depressiven Erkrankung, deren Auslöser und möglichen Therapieansätzen beschäftigen.

Studie I mit dem Titel " **Childhood adversity and cognitive functioning in patients with major depression**" untersuchte den potentiellen Zusammenhang zwischen frühen traumatischen Kindheitserlebnissen und der kognitiven Leistungsfähigkeit bei Patienten mit Major Depression. Zahlreiche klinische und experimentelle Studien weisen bislang bei einigen, aber nicht bei allen Patientinnen und Patienten[1] mit Major Depression auf eine Veränderung der Gedächtnis- und exekutiven Funktionen hin. In Studie I der vorliegenden Arbeit konnte aufgezeigt werden, dass eine erhöhte Anzahl erlebter negativer Kindheitserfahrungen mit späterem Allgemeinwissen, der Verarbeitungsgeschwindigkeit sowie exekutiven Funktionen bei Patienten mit Major Depression assoziiert sein könnte. Vor allem körperlicher Missbrauch und Vernachlässigung in der Kindheit scheinen mit späteren Defiziten in den Bereichen verbales Lernen und exekutive Funktionen einherzugehen.

In **Studie II** mit dem Titel „**Cognitive behavioral therapy improves recognition memory in major depression: Results of a randomized controlled trial**" interessierte zum einen, ob sich depressive Patienten im Vergleich zu einer geschlechts- und altersgematchten gesunden Kontrollgruppe in ihren Gedächtnisfunktionen unterscheiden. Zum anderen wurden potentielle Verbesserungsmöglichkeiten beeinträchtigter Gedächtnisfunktionen durch eine 4-monatige kognitive Verhaltenstherapie untersucht. Es zeigte sich, dass kognitive Verhaltenstherapie in Kombination mit regelmäßiger sportlicher Betätigung sowie kognitive Verhaltenstherapie in Kombination mit achtsamkeitsbasierten, angenehmen Aktivitäten mit einer Verbesserung der mnestischer Funktionen depressiver Patienten assoziiert sein könnte. Im Bereich Wiedererkennensleistung konnte über den Verlauf einer 16-wöchigen Behandlung eine signifikante Leistungssteigerung erzielt werden, welche zumindest teilweise eine Reversibilität von beeinträchtigten Gedächtnisfunktionen nahelegt.

Studie III mit dem Titel "**The predictive value of somatic and cognitive depressive symptoms for cytokine changes in patients with major depression**" schließlich

betrachtete psychobiologische Aspekte einer depressiven Erkrankung genauer und differenziert zwischen *kognitiven* und *somatischen* Symptom-Dimensionen von Depression. Dabei zeigte sich, dass langanhaltende somatische, nicht aber kognitiv-affektive depressive Symptome, mit einem Anstieg von pro-inflammatorischen Zytokinen bei Frauen mit Major Depression in Zusammenhang stehen. Diese Ergebnisse lassen vermuten, dass Symptom-Dimensionen einer Major Depression (somatische oder kognitiv-affektive Symptome) unterschiedlich mit immunologischen Veränderungen assoziiert sein könnten.

[1]Aus Gründen der Lesbarkeit wird im Folgenden ausschließlich die männliche Form verwendet.

1.2. Abstract

Major Depression (MD) is a heterogeneous disorder associated with neuropsychological and immunological features. The present cumulative dissertation including three peer-reviewed articles addresses different symptom-dimensions of major depression, potential causes and therapeutic approaches.

In **article I** "**Childhood adversity and cognitive functioning in patients with major depression**" we examined the potential association between early adversities and cognitive and executive functioning in patients with MD. Although Major depression is often accompanied by deficits in cognitive functioning and lowered executive functions, not all depressed patients show impairments in these domains. The present study suggests that the overall number of traumas of depressive patients was significantly associated with poorer general knowledge, lower processing speed and impaired executive functions. Particularly an association between physical neglect and poorer verbal learning, and physical abuse and diminished executive functions was assumed.

Article II „Cognitive behavioral therapy improves recognition memory in major depression: Results of a randomized controlled trial" examined whether cognitive behavioral therapy (CBT) improves verbal learning and memory in patients with MD. A second aim was to learn whether emphasizing physical exercise during behavioral activation has additional effects on verbal performance. When compared to a waiting list control group, CBT emphasizing exercise during behavioral activation and CBT with pleasurable low-energy activities as an active control condition were associated not only with reduced depressive symptom severity but also with improved recognition memory after treatment.

These results contradict in part previous assumptions that cognitive impairments persists despite depressive symptom reduction.

Article III titled "**The predictive value of somatic and cognitive depressive symptoms for cytokine changes in patients with major depression**" suggests that ''cognitive-affective'' and ''somatic'' symptom-dimensions are differently related to immune function in patients with Major Depression. Our results indicate that higher somatoform symptoms during the last 2 years might predict an increase in TNF-alpha in women with major depression. A subtype of MD, associated with especially somatic symptoms might be hypothesized.

2. Theoretischer Hintergrund

2.1. Erscheinungsbild der Major Depression

Die Major Depression (MD) ist eine hoch prävalente Störung (Kessler et al., 2005), von welcher laut Weltgesundheitsorganisation (WHO) zum aktuellen Zeitpunkt etwa 350 Millionen Menschen weltweit betroffen sind. Die Betroffenen erleben als Hauptsymptome Niedergeschlagenheit, einen Verlust von Freude und Interesse und Antriebslosigkeit, daneben auch Schuldgefühle, einen verminderten Selbstwert, Schlafstörungen, Appetitverlust oder eine verminderte Konzentrationsfähigkeit. Fast eine Million Menschen begehen aufgrund einer depressiven Erkrankung jährlich Suizid (World Federation For Mental Health (WFMH), 2012). Die Lebenszeitprävalenz einer diagnostizierten Major Depression beträgt in Deutschland 11,6%; die 12-Monats-Prävalenz liegt bei 6,0% (Busch, Maske, Ryl, Schlack, & Hapke, 2013). Der Verlauf der Störung ist in vielen Fällen rezidivierend: 75% der betroffenen Personen erleben nach Remission einer Episode mindestens eine weitere depressive Phase (Richards, 2011). Zudem belegen Zahlen von deutschen Krankenkassen, dass neben dem Leid für die Betroffenen auch direkte und indirekte Kosten für die Gesellschaft entstehen. So sind 7,1% aller erfassten Fehltage in Deutschland auf eine Major Depression zurückzuführen (Grobe & Steinmann, 2015).

Dabei stellt die Major Depression ein durchaus heterogenes Störungsbild dar und ist durch eine Vielzahl unterschiedlicher Symptome gekennzeichnet. Differenzieren lassen sich somatisch/vegetative, verhaltensbezogene, affektive, motivationale sowie kognitive/gedächtnisbezogene Symptome, welche bei Patienten in unterschiedlicher Ausprägung und Zusammensetzung auftreten (Hautzinger, 2013). Darüber hinaus werden die Schwere einer depressiven Erkrankung (leicht, mittelgradig, schwer) und der Zeitpunkt der ersten depressiven Episode (early-onset, late-onset) als mögliche Unterscheidungsmerkmale betrachtet (Korten, Comijs, Lamers, & Penninx, 2012; Lamers et al., 2010). Die Literatur differenziert Subtypen wie die atypische oder melancholische Depression oder die Depression mit psychotischen Merkmalen und klassifiziert nach Polarität (unipolar oder bipolar) (Gili et al., 2012; Parker, 2005; Porter, Bourke, & Gallagher, 2007; Thase, 2013). Auch biologische Differenzierungen werden vorgenommen: so sind verschiedene Symptom-Dimensionen (somatische oder kognitiv-affektive Symptome) von Depression mit unterschiedlichen immunologischen Aspekten assoziiert (Duivis, Vogelzangs, Kupper, de Jonge, & Penninx, 2013; Euteneuer et al., 2012) und biologische Subtypen, wie etwa ein

„inflammatorischer“ Subtyp der MD werden diskutiert (Gallagher, Kiss, Lanctot, & Herrmann, 2016; Jokela, Virtanen, Batty, & Kivimäki, 2016; Miller & Raison, 2015).

Bei der Pathogenese einer Major Depression spielen viele unterschiedliche Einflussfaktoren eine Rolle und ein multifaktorielles Entstehungsmodell ist anzunehmen (Brakemeier, Schramm, & Hautzinger, 2012). Sowohl biologische (genetische, physiologische, hormonelle, immunologische oder anatomische) wie auch psychologische (Selbstwertprobleme, Lerndefizite, frühe Bindungsstörungen) Einflussfaktoren sind bei der Entwicklung der Major Depression und ihr zugehöriger möglicher Subtypen mit einzubeziehen. Darüber hinaus sind umweltbezogene (Traumata, Mangel an Verstärkung, ungünstige Sozialisationsbedingungen) Faktoren von Interesse: Vor allem frühkindliche, belastende Stresserfahrungen und deren differentieller Einfluss auf die spätere Entwicklung depressiver Symptome sind Gegenstand zahlreicher Studien (Kessler et al., 2010). So scheinen soziale Deprivation, Vernachlässigung, Misshandlungen oder Erfahrungen der Nichtkontrolle möglicherweise veränderte physiologische Reaktionsmuster oder Verhaltens- und kognitive Defizite mit zu bedingen (Brakemeier et al., 2012; Gould et al., 2012; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Van Veen et al., 2013).

Die Identifikation von Subtypen der Major Depression, basierend auf Symptomprofilen oder klinischen und biologischen Korrelaten der MD ist für ein besseres Verständnis der Pathogenese der MD unabdingbar. Die Untersuchung möglicherweise zu differenzierender Symptom-Dimensionen und Subtypen mag die Entwicklung von entsprechend angepassten individuellen Behandlungsmöglichkeiten fördern, was vor dem Hintergrund der hohen Anzahl Betroffener hoch relevant erscheint. Die vorliegende Arbeit soll aus diesem Grund zu einem besseren Verständnis des so heterogenen Störungsbildes Major Depression beitragen. Sie befasst sich mit dem Symptombereich neuropsychologischer Defizite, dem Einfluss von frühen, belastenden Stresserfahrungen auf mnestische Funktionen sowie Veränderungsmöglichkeiten dieser. Darüber hinaus sollen somatische und kognitiv-affektive Symptom-Dimensionen und deren differentieller Einfluss auf immunologische Veränderungen im Rahmen einer MD untersucht werden.

2.2. Neuropsychologische Veränderungen bei Major Depression

Metaanalysen zeigen kognitive Defizite als ein häufiges Symptom im Rahmen der Major Depression (Rock, Roiser, Riedel, & Blackwell, 2014; Snyder, 2013). Diese können sowohl die Lebensqualität als auch die Therapiefähigkeit und den Behandlungserfolg un-

günstig beeinflussen (Bortolato, Carvalho, & McIntyre, 2014; Cotrena, Branco, Shansis, & Fonseca, 2016; Dunkin et al., 2000). Gleichzeitig scheinen nicht alle an MD erkrankten Patienten an kognitiven Einschränkungen zu leiden. Bisherige Studien präsentieren inkonsistente Befunde und lassen vermuten, dass möglicherweise nur Subgruppen von Patienten mit einer MD kognitive Einschränkungen erleben (Gualtieri & Morgan, 2008).

Bisherige Studien diesbezüglich befassen sich vor allem mit Gedächtnis- und exekutiven Funktionen depressiver Patienten. *Gedächtnisfunktionen* umfassen Informationsaufnahme, Enkodierung (Einspeicherung), Konsolidierung (Festigung), Ablagerung und den Abruf von Informationen (Brand & Markowitsch, 2004). *Exekutive Funktionen* beschreiben kognitive Prozesse, welche durch Kontrolle, Steuerung und Koordination verschiedener Subprozesse das Erreichen von übergeordneten Zielen ermöglichen. Solche Subprozesse sind etwa kognitive Flexibilität, Planen und Entscheiden, Inhibition oder Monitoring. Auch das Arbeitsgedächtnis kann hier zugeordnet werden (Seiferth, Thienel, & Kircher, 2007).

Hinsichtlich des Zusammenhangs von *Gedächtnisfunktionen* und Major Depression sprechen einige Befunde für eine Einschränkung des verbalen und visuellen sowie des visuell-räumlichen Gedächtnisses (Hammar & Ardal, 2009; Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Lin et al., 2014; R. J. Porter, 2003), wobei depressive Patienten des melancholischen Subtyps stärker beeinträchtigt zu sein scheinen als Patienten des atypischen Subtyps (Beckmann Bosaipo, Paula, Young, & Francisco, 2017; Zaninotto et al., 2016). Gleichzeitig zeigen sich bei einigen Autoren keine Beeinträchtigungen im Bereich Gedächtnis in depressiven Stichproben. So vermuten beispielsweise Wang und Kollegen keine Unterschiede zwischen depressiven Patienten und Gesunden hinsichtlich des verbalen Gedächtnisses (Wang et al., 2006). Auch bei Halvorsen und Kollegen finden sich keine signifikanten Unterschiede in Bezug auf Gedächtnisfunktionen zwischen depressiven Patienten und gesunden Kontrollpersonen (Halvorsen, Waterloo, Sundet, Eisemann, & Wang, 2011). Sweeney et al. fanden bei Patienten mit Major Depression nur im Bereich des episodischen Gedächtnisses signifikante Beeinträchtigungen, die verbalen Gedächtnisfunktionen waren im Vergleich zu Gesunden nicht signifikant verändert (Sweeney, Kmiec, & Kupfer, 2000). Ebenfalls nicht eindeutig sind die Aussagen hinsichtlich Veränderungen *exekutiver Funktionen* bei Patienten mit Major Depression. Naismith und Kollegen zeigten eine Beeinträchtigung depressiver Patienten in Bezug auf Problemlösen, Planen und Arbeitsgedächtnis im Vergleich zu Gesunden (Naismith et al., 2003), während Chamberlain und Sahakian Veränderungen im Bereich „Entscheidungen treffen“ vermuten

(Chamberlain & Sakakian, 2006). Weitere Befunde sprechen für verminderte Leistungen im Bereich des Arbeitsgedächtnis depressiver Patienten (Egeland et al., 2003; Taylor Tavares et al., 2007). Unveränderte Leistungen hinsichtlich exekutiver Funktionen zeigte dagegen die Untersuchung von Grant und Kollegen an einer Stichprobe von 123 depressiven Patienten (Grant, Thase, & Sweeney, 2001).

Zusammenfassend lässt sich festhalten, dass sich die Literatur in Bezug auf Gedächtnis- und exekutive Funktionen bei depressiven Patienten inkonsistent zeigt: nur eine Subgruppe von Patienten mit einer MD scheint kognitive Einschränkungen zu erleben. Weitere Forschung hierzu scheint von großem Interesse. Ein möglicher Vulnerabilitätsfaktor für die Entwicklung kognitiver Defizite im Rahmen einer Major Depression sind möglicherweise frühe massive Stresserfahrungen (Kindheitstraumatisierungen) (Gould et al., 2012), auf welche im nächsten Abschnitt detaillierter eingegangen werden soll.

2.3. Kindheitstraumatisierung und Major Depression

Bei vielen psychisch kranken Patienten lassen sich ungünstige Sozialisationsbedingungen sowie massive Stresserfahrungen in der Kindheit in der Anamnese finden und eine Einteilung von psychopathologischen Subtypen basierend auf erlebten frühen Stresserfahrungen wird diskutiert (Teicher & Samson, 2013). Weitere Befunde lassen vor allem einen Zusammenhang zwischen frühen traumatischen Lebensereignissen und einer späteren Major Depression vermuten (Kessler 1997, Kendler 2004). Definiert werden *Kindheitstraumatisierungen* als frühe interpersonelle Gewalterfahrungen in Form von emotionalem, körperlichem und sexuellem Missbrauch sowie emotionaler und körperlicher Vernachlässigung (Bernstein et al., 1994). Meta-analytische Ergebnisse zeigen, dass vor allem sexuelle und körperliche Gewalt in der Kindheit mit höheren Depressionserkrankungsraten bei Erwachsenen einhergehen (Lindert et al., 2013). Aber auch Zusammenhänge zwischen emotionalem Missbrauch in der Kindheit und einer späteren depressiven Erkrankung konnten aufgezeigt werden (Shapero et al., 2014). Frühkindliche Stresserfahrungen scheinen zudem mit einem möglichen früheren Beginn, einer höheren Anzahl depressiver Episoden sowie einem eher chronischen Verlauf der Major Depression assoziiert zu sein (Gillespie & Nemeroff, 2005; Klein et al., 2009). Darüber hinaus scheinen Kindheitstraumatisierungen einen schlechteren Behandlungsverlauf vorherzusagen (Nanni, Uher & Danese, 2012).

2.3.1. Kindheitstraumatisierung und Gedächtnisfunktionen

Neben einem erhöhten Risiko für psychische Erkrankungen ist ein Zusammenhang von Kindheitstraumatisierungen mit späteren beeinträchtigten Gedächtnis- und Exekutivfunktionen zu vermuten. Majer und Kollegen konnten in einer gesunden Stichprobe zeigen, dass emotionaler Missbrauch und körperliche Vernachlässigung in der Kindheit mit schlechterer Gedächtnisleistung im Erwachsenenalter assoziiert zu sein scheinen (Majer, Nater, Lin, Capuron, & Reeves, 2010). Ähnliches lässt sich bei Spann und Kollegen finden, welche in einer ebenfalls gesunden Stichprobe einen Zusammenhang zwischen körperlicher Gewalt und Vernachlässigung in der Kindheit und reduzierter kognitiver Flexibilität im Erwachsenenalter vermuten (Spann et al., 2012). Aas und Kollegen fanden in einer Stichprobe mit schizophrenen Patienten verminderte Fähigkeiten im Arbeitsgedächtnis und in Bereich der exekutiven Funktionen, wenn diese körperlichen Missbrauch in der Kindheit erlebt hatten (Aas et al., 2012). Die Befunde für depressive Patienten sind noch rar, erste Hinweise gibt es jedoch für mögliche Zusammenhänge zwischen Kindheitstraumatisierungen und kognitiven/neuropsychologischen Symptomen im Rahmen einer MD (Gould et al., 2012; Vares et al., 2016).

Eine mögliche Erklärung für die Assoziation von Vernachlässigung und Missbrauch in der Kindheit und späteren kognitiven Einbußen im Rahmen einer Major Depression bieten neben psychosozialen Einflussfaktoren möglicherweise Veränderungen neurobiologischer Systeme. Diskutiert und untersucht werden in diesem Zusammenhang Mechanismen des neuroendokrinologischen Feedback-Systems der Hypothalamus-Hypophysen-Nebennierenrinden-Achse (engl. hypothalamic-pituitary-adrenal axis: HPA-Achse) sowie strukturelle Veränderungen im Gehirn und Entzündungsprozesse.

Frühe Stresserfahrungen scheinen die Aktivität der HPA-Achse zu modulieren, wobei Dauer, Art und Zeitpunkt erlebter Kindheitstraumatisierungen hierbei differentielle Einflüsse zu haben scheinen (Carpenter, Shattuck, & Price, 2011). Heim und Kollegen zeigten bei depressiven Frauen mit berichtetem Missbrauch in der Kindheit stärkere Kortisol-Ausschüttungen als Reaktion auf Stress als bei Patientinnen ohne Missbrauch (Heim et al., 2000), während nachfolgende Studien eine reduzierte Kortisolantwort bei Patienten mit Kindheitstraumatisierungen vermuten (Carpenter et al., 2011; Tyrka, Burgers, Philip, Price, & Carpenter, 2013).

Bildgebende Verfahren weisen auf mögliche Effekte von Kindheitstraumatisierungen auf die Gehirnstruktur- und konnektivität hin (Teicher, Samson, Anderson, & Ohashi, 2016). Vor allem reduzierte Hippocampi-Volumen bei depressiven Patienten mit in der

Kindheit erlebter Gewalt werden diskutiert (Carrion, Victor G, Weems, Richert, Hoffmann, & Reiss, 2010; Carrion, Weems, & Reiss, 2007;Vythilingam et al., 2002).

Eine weitere Rolle im Hinblick auf durch Stresserfahrungen veränderte neurobiologische Systeme spielen möglicherweise Entzündungsprozesse. So zeigen missbrauchte oder sozial isolierte Kinder im Erwachsenenalter signifikant höhere Entzündungswerte als Vergleichskinder (Danese et al., 2013; Slopen, Kubzansky, McLaughlin, & Koenen, 2013). Erhöhte Entzündungsparameter wiederum werden in Bezug auf Lernen und Gedächtnis, synaptische Plastizität und Neurogenese als relevant diskutiert (Monteiro et al., 2016). Erhöhte Interleukin-6 Spiegel scheinen mit reduzierten Lern- und Gedächtnisfunktionen einherzugehen (Grassi-Oliveira, Bauer, Pezzi, Teixeira, & Brietzke, 2011) und auch die Neurogenese, bedeutsam in der Konsolidierung von Gedächtnisinhalten, zu beeinflussen (McAfoose & Baune, 2009). Monteiro und Kollegen konnten zudem zeigen, dass eine Blockade von Interferon-gamma die dorsale Hippocampusstruktur sowie die Zelldichte und die synaptische Plastizität positiv beeinflussen kann. Diese Veränderungen wiederum scheinen mit einer Verbesserung von Lern- und Gedächtnisfunktionen einherzugehen (Monteiro et al., 2016).

Neben neurobiologischen Einflussfaktoren sind mögliche psychosoziale Mechanismen relevant. Ungesunde, nicht ausreichende Ernährung oder Übergewicht beeinflussen möglicherweise neuronale Funktionen (McCarthy-Jones & McCarthy-Jones, 2014; Meeusen, 2014). Daneben zeigen Gewalt ausgesetzte Kinder häufiger verminderte Emotionsregulationsfähigkeiten, Entwicklungsauffälligkeiten und verbal oder physisch aggressives oder impulsives Verhalten, welches zum einen das Risiko weiterer Gewalterfahrungen erhöhen kann (Cloitre, Stovall-McClough, Zorbas, & Charuvastra, 2008; Hadianfard, 2014; Sullivan & Knutson, 2000) und zum anderen Konzentrations- und Gedächtnisdefizite sowie eine weniger gute Bildung bedingen mag (Romano, Babchishin, Marquis, & Frechette, 2015).

Insgesamt lässt sich festhalten, das früher, massiver Stress über psychosoziale und neurobiologische Mechanismen sowie funktionale und strukturelle Veränderungen in bestimmten Hirnregionen sowohl an der Pathogenese der Major Depression als auch an Veränderungen kognitiver Fertigkeiten beteiligt sein könnte. Unklar ist bisher, ob und in welchem Ausmaß Kindheitstraumatisierungen kognitive Defizite im Rahmen einer Major Depression erklären können.

2.4. Einflussmöglichkeiten auf neuropsychologische Veränderungen im Rahmen einer MD

Betrachtet man den Verlauf neuropsychologischer Defizite während einer Remission depressiver Symptome, so zeigen sich auch hier inkonsistente Befunde: Im Sinne einer "trait"- Hypothese berichten einige Autoren von anhaltenden kognitiven Defiziten trotz deutlicher Symptomreduktion bei depressiven Patienten (Hammar et al., 2003; Portella et al., 2003; Neu et al., 2005). Andere Studien dagegen zeigen dagegen eine Verbesserung kognitiver Fähigkeiten einhergehend mit der Remission einer depressiver Störung auf (siehe Austin et al., 2001 und Hasselbalch, Knorr, & Kessing, 2011 für eine Übersicht; Deuschle et al., 2004). Die Autoren der letztgenannten Ergebnisse betrachten neuropsychologische Veränderungen im Rahmen einer Major Depression somit als zumindest teilweise reversibel und argumentieren im Sinne einer „state"-Hypothese.

Bisherige Studien, welche sich mit möglichen Veränderungen von neuropsychologischen Fähigkeiten während einer depressiven Erkrankung befassen, untersuchten bislang vor allem medikamentöse Behandlungsformen. Herrera-Guzmán und Kollegen beispielsweise zeigten eine Verbesserung des verbalen und visuellen Gedächtnisses nach einer Behandlung mit Antidepressiva auf (Herrera-Guzmán et al., 2009). Auch Biringer und Kollegen konnte einen Anstieg der verbalen Gedächtnisfunktionen nach erfolgreicher Behandlung mit Antidepressiva bei depressiven Patienten beobachten (Biringer et al. 2007). Ein weiterer Ansatz, um neuropsychologischen Defiziten im Rahmen einer Major Depression zu begegnen, sind spezielle "kognitive Trainings": Oertel-Knöchel und Kollegen konnten durch ein solches signifikante Verbesserungen in den Bereichen Arbeitsgeschwindigkeit, Arbeitsgedächtnis und visuelles Lernen nachweisen (Oertel-Knöchel et al., 2014).

2.4.1. Psychotherapeutische Ansätze in der Behandlung neuropsychologischer Defizite

Studien, die sich mit dem Einfluss psychotherapeutischer Ansätze auf neuropsychologische Fähigkeiten befassen, sind bisher noch rar. Zum aktuellen Zeitpunkt gibt es eine explorative Untersuchung zum Einfluss von metakognitiver Therapie (MKT) bzw. kognitiver Verhaltenstherapie (KVT) auf Gedächtnisfunktionen, welche eine Verbesserung in den Bereichen Arbeitsgedächtnis und Aufmerksamkeit durch die genannten Therapieansätze nachweisen konnte (Groves et al., 2015). Eine randomisierte, kontrollierte Studie von Bastos und Kollegen zeigte eine Verbesserung in Bezug auf Leistungen in der „Wechsler

Adult Intelligence Scale“ nach Behandlung mit psychodynamischer Psychotherapy und deren Kombination mit Antidepressiva bei depressiven Patienten auf (Bastos, Pinto Guimarães, & Trentini, 2013).

Obwohl sich KVT als wirksame Therapiemethode in der Behandlung depressiver Störungen etabliert hat (Cuijpers et al., 2013), ist ihr Effekt auf mnestische Funktionen im Rahmen einer MD kaum untersucht. Die bisher einzige randomisierte kontrollierte Studie zum Einfluss von KVT auf neuropsychologische Funktionen von Porter und Kollegen fand keine Verbesserung im Bereich verbales Lernen und Gedächtnis, Aufmerksamkeit oder exekutive Funktionen (Porter et al., 2016).

Studien zur Wirksamkeit von kognitiver Verhaltenstherapie betonen den positiven Effekt von Verhaltensaktivierung als eine Komponente der KVT (Dimidjian et al., 2006). Zudem zeigen bisherige Forschungsarbeiten, dass Verhaltensaktivierung vor allem in Form von regelmäßiger, moderater Bewegung positive Effekte auf die Schwere einer depressiven Erkrankung haben kann (Cooney et al., 2013). Neben positiven Effekten auf depressive Symptome, scheinen auch kognitive Fertigkeiten durch physische Aktivität verbessert werden zu können (Chang, Labban, Gapin, & Etnier, 2012; Colcombe & Kramer, 2003; Smith et al., 2011). Studien, welche Verhaltensaktivierung als Element der KVT und deren Wirkung auf kognitive Defizite untersuchen, gibt es bisher jedoch nicht.

Zusammenfassend lässt sich festhalten, dass sich die Literatur in Bezug auf Gedächtnis- und exekutive Funktionen bei depressiven Patienten inkonsistent zeigt und einige, nicht aber alle Patienten mit einer MD kognitive Einschränkungen zu erleben scheinen. Die Untersuchung von Mechanismen, welche bei Subgruppen depressiver Patienten neuropsychologische Veränderungen bedingen ist somit höchst relevant. Kindheitstraumatisierungen als möglicher Einflussfaktor auf neuropsychologische Veränderungen werden diskutiert, Befunde hierzu sind jedoch noch rar. Ebenfalls inkonsistent zeigen sich Studien bezüglich einer möglichen Reversibilität neuropsychologischer Einschränkungen und der Einfluss kognitiver Verhaltenstherapie in Kombination mit Verhaltensaktivierung auf neuropsychologische Defizite ist noch kaum untersucht.

2.5. Major Depression und psychoneuroimmunologische Prozesse

Der Einfluss von Immunprozessen auf die Pathogenese und Phänomenologie psychischer Störungen, insbesondere auf die Major Depression, wird seit längerem untersucht. Von Bedeutung scheinen hierbei vor allem entzündungsfördernde (pro-inflammatorische) Zy-

tokine zu sein, deren erhöhte Konzentration im Zusammenhang mit Major Depression in meta-analytischen Befunden bestätigt wurde (Dowlati et al., 2010; Köhler et al., 2017).

Vermutet wird hierbei bisher ein bi-direktionaler Zusammenhang: Studien, welche sich mit Zytokin-Therapien, etwa zur Behandlung von Krebs oder chronischen viralen Infektionen beschäftigen, zeigen depressive Symptome als Behandlungsnebenwirkung auf (Bull et al., 2009; Charles L. Raison, Capuron, & Miller, 2006; Udina et al., 2012). Meta-analytische Befunde zeigen zudem, dass anti-entzündliche Behandlungsansätze (z.B. Gabe von TNF-alpha-Antagonisten) mit einer antidepressive Wirkung einhergehen können (Köhler et al., 2014). Auch tierexperimentelle Studien belegen, dass die Gabe pro-inflammatorischer Zytokine zu depressions-ähnlichem Verhalten führen kann (reduziertes Explorationsverhalten, sozialer Rückzug, reduzierte Aktivität) (Carmichael et al., 2006; O´Connor et al., 2009).

Umgekehrt zeigen einige prospektive Studien, dass nicht nur Entzündungsprozesse die Pathogenese einer Major Depression begünstigen, sondern auch die depressive Erkrankung selbst möglicherweise eine Veränderung immunologischer Prozesse bewirkt (Kiecolt-Glaser, Derry, & Fagundes, 2015). So konnten Stewart und Kollegen in einer längsschnittlichen Untersuchung über 6 Jahre zeigen, dass die Symptomschwere einer depressiven Erkrankung eine Anstieg von Interleukin-6 (Il-6) im Serum vorhersagt (Stewart, Rand, Muldoon, & Kamarck, 2009). Weitere prospektive Studien zeigen einen möglichen Zusammenhang zwischen depressiven Episoden und einem späteren höheren Level des akut-Phase-Proteins C-reaktives Protein (CRP) auf (Copeland, Shanahan, Worthman, Angold, & Costello, 2013; Deverts et al., 2011; Matthews, Schott, Brombergere, Cyranowski, & Sowers, 2010).

2.5.1 Symptom-Dimensionen der Major Depression und immunologische Veränderungen

Trotz zahlreicher Belege für veränderte Immunprozesse im Rahmen eine Major Depression, zeigen nicht alle depressiven Patienten ein verändertes immunologisches Profil: Raison und Miller vermuten, dass nur etwa ein Drittel der depressiven Patienten veränderte Immunparameter aufweisen und Daten des *National Health and Nutrition Examination Survey* zeigten bei 47% der untersuchten depressiven Patienten erhöhte Spiegel des akut-Phase-Proteins C-reaktives Protein (CRP) (Raison & Miller, 2011; Rethorst, Bernstein, & Trivedi, 2014). Erhöhte Entzündungswerte werden zudem insbesondere bei Patienten mit späterem Beginn der Depression („late-onset depression“) vermutet. Analysen des *Natio-*

nal Health and Nutrition Examination Survey legen nahe, dass ein späterer Depressionsbeginn mit subklinischen vaskulären Prozessen assoziiert sein könnte (Vogelzangs et al., 2012). Eine solche mögliche "inflammatorische" Subgruppe depressiver Patienten scheint mehr somatische Komorbiditäten sowie weniger günstige Krankheitsverläufe zu erleben (Gallagher et al., 2016).

Bisherige Studienergebnisse lassen vermuten, dass "kognitiv-affektive" und "somatische" Symptom-Dimensionen der Major Depression unterschiedlich mit immunologischen Veränderungen assoziiert sein könnten. Zu den kognitiv-affektiven Symptomen zählen u.a. Niedergeschlagenheit, Schuldgefühle oder der Verlust von Interesse, während die somatische Symptom-Dimension u.a. Schlafstörungen, Appetitverlust oder Erschöpfung beinhaltet (Kupper, Widdershoven, & Pedersen, 2012). Höhere Spiegel von Entzündungsparametern scheinen eher mit Symptombereichen assoziiert zu sein, welche das sogenannte „sickness behavior" charakterisieren und der somatischen Symptom-Dimension zuzuordnen sind (Jokela et al., 2016; Miller & Raison, 2015). Auch eine Untersuchung von Duivis und Kollegen lässt vermuten, dass lediglich somatische Aspekte einer Major Depression, nicht aber kognitiv-affektive Symptome mit erhöhten Spiegeln von CRP, Interleukin-6 und Tumor-Nekrose-Faktor-alpha einhergehen (Duivis et al., 2013). Auch scheinen vor allem somatische Symptom-Dimensionen von Depression auf kardiovaskuläre Erkrankungen einen prädiktiven Einfluss zu haben (Jonge, Mangano, & Whooley, 2007; Linke et al., 2009; Myint et al., 2007; Schiffer et al., 2009; Smolderen & Spertus, 2009). Zudem stehen somatische, nicht aber kognitiv-affektive depressive Symptome im Zusammenhang mit verminderter Herzratenvariabilität und reduzierter Baroreflex Sensitivität (Bosch et al., 2009; Jonge et al., 2007). Arbeiten unserer eigenen Arbeitsgruppe zeigten, dass bei Patienten mit MD erhöhte Spiegel von löslichen Interleukin-2 Rezeptoren mit somatischen Aspekten einer MD assoziiert sind, nicht aber mit kognitiv-affektiven depressiven Symptomen (Euteneuer et al., 2012).

Insgesamt gilt es einen möglichen Einfluss von MD auf immunologische Veränderungen anhand von prospektiven Studien weiter zu untersuchen. Forschung in Bezug auf einen möglichen „inflammatorischen Subtyp" der Major Depression und eine differenzierte Erfassung mit diesem assoziierter Symptome scheint darüber hinaus relevant, um eine genaue Diagnostik und entsprechend angepasste Behandlungsmöglichkeiten zu ermöglichen.

3. Darstellung des Dissertationsvorhaben

3.1. Überblick

Die in Studie I vorgestellten Ergebnisse beruhen auf Daten einer randomisiert-kontrollierten klinischen Interventionsstudie (DFG-Geschäftszeichen Ri 574/13) unter der Leitung von Prof. Dr. W. Rief. Die Daten von Studie 2 und 3 der Dissertation entstammen einer randomisiert-kontrollierten klinischen Interventionsstudie, die ebenfalls unter der Leitung von Prof. Dr. W. Rief von Mai 2011 bis August 2015 in der Psychotherapie-Ambulanz Marburg durchgeführt wurde (DFG Geschäftszeichen Ri 574/23-1).

3.2. Relevanz und Herleitung der Fragestellung

Über die letzten Jahrzehnte hinweg beschäftigt sich die klinische Forschung ausführlich mit depressiven Erkrankungen und einem besseren Verständnis dieses recht heterogenen Störungsbildes. Neben einer Veränderung des Affekts und des Antriebs, sind Patienten auch von neuropsychologischen Einschränkungen betroffen, welche das Funktionsniveau maßgeblich beeinflussen können (Bortolato et al., 2014). Wie eingangs dargestellt, zeigen sich die bisherigen Befunde hierzu jedoch inkonsistent und nicht alle Patienten sind von solchen neuropsychologischen Defiziten betroffen. Als ein möglicher Vulnerabilitätsfaktor für die Entwicklung kognitiver Defizite werden frühe massive Stresserfahrungen (Kindheitstraumatisierungen) diskutiert. Diese bedingen möglicherweise immunmodulatorische Veränderungen oder nehmen Einfluss auf die neuronale Plastizität, was wiederum spätere kognitive Veränderungen bedingen mag (Majer et al., 2010). Kaum untersucht sind jedoch bisher mögliche Zusammenhänge zwischen Kindheitstraumatisierungen und neuropsychologischen Defiziten bei depressiven Patienten. Eine erste Studie hierzu von Gould und Kollegen, liefert mögliche Hinweise darauf, dass Kindheitstraumatisierungen spätere Unterschiede hinsichtlich neuropsychologischer Defizite bei depressiven Patienten erklären können (Gould et al., 2012). Inkonsistent sind zudem die bisherigen Befunde hinsichtlich einer möglichen Verbesserung neuropsychologischer Defizite. Während einige Studien eine Reversibilität kognitiver Defizite bei Remission der Depression annehmen lassen (Deuschle et al., 2004; Hasselbalch et al., 2011), sprechen andere Befunde für kognitive Defizite als von der Remission einer Depression unabhängige und anhaltende Einschränkungen (Portella et al., 2003). Studien zu Behandlungsansätzen, welche eine Verbesserung neuropsychologischer Defizite anstreben sind bisher noch rar und beschränken sich weitestgehend auf medikamentöse Verfahren oder kognitive Trainings (Biringer et al., 2007;

Knöchel et al., 2012). Inwieweit psychotherapeutische Verfahren einen Einfluss auf neuropsychologischer Defizite depressiver Patienten haben können, ist kaum untersucht. Die bislang einzige randomisierte, kontrollierte Studie zum Einfluss kognitiver Verhaltenstherapie (KVT) als wirksame Therapieform bei Major Depression (Cuijpers et al., 2013), fand keinen Effekt auf Gedächtnisfunktionen (Porter et al., 2016). Unklar ist bisher auch, ob die Art der Verhaltensaktivierung im Rahmen der KVT eine Rolle bei der Behandlung der MD sowie der Reversibilität von beeinträchtigten Gedächtnisfunktionen spielt. Verhaltensaktivierung in Form von regelmäßiger, moderater sportlicher Betätigung zeigte sich in bisherigen Studien als antidepressogen (Cooney et al., 2013) und auch auf kognitive Fertigkeiten scheint physische Aktivität positiven Einfluss nehmen zu können (Chang et al., 2012; Colcombe & Kramer, 2003; Smith et al., 2011). Eine differenzierte Betrachtung der Einflussmöglichkeiten von KVT wie auch Methoden der Verhaltensaktivierung (z.B. Sport) auf Gedächtnisfunktionen scheint somit höchst relevant und weitere Forschung dringend erforderlich.

Eine stetig wachsende Zahl an Studien liefert Evidenz für die Beteiligung von Immunprozessen an der Pathogenese von Depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Kiecolt-Glaser et al., 2015), wobei bislang von einem bidirektionalen Zusammenhang auszugehen ist. Erste Studien lassen vermuten, dass Symptom-Dimensionen einer Major Depression (somatische oder kognitiv-affektive Symptome) unterschiedlich mit immunologischen Veränderungen assoziiert sind (Kupper et al., 2012). Prospektive Studien, welche den differentiellen Einfluss depressiver Symptomen auf Immunparameter untersuchen, sind daher von großer Relevanz.

3.3. Ziele und Hypothesen der Dissertation

Basierend auf der bisherigen Forschungslage wurden dem Dissertationsvorhaben folgende Zielsetzungen und Fragestellungen zu Grunde gelegt:

Ziel von Studie I der Dissertation war es, einen möglichen Zusammenhang von Kindheitstraumatisierungen und kognitiven Defiziten im Rahmen einer Major Depression aufzuzeigen. Hierbei wurden verschiedene Arten von Traumatisierungen erfasst und deren differentielle Auswirkungen auf die kognitive Leistungsfähigkeit depressiver Patienten untersucht.

In Studie II wurde eine mögliche Reversibilität kognitiver Defizite im Rahmen einer viermonatigen kognitiven Verhaltenstherapie überprüft. Zusätzlich wurden mögliche

additive positive Effekte auf Gedächtnisfunktionen durch eine Kombination von KVT mit Verhaltensaktivierung durch regelmäßige Bewegung oder angenehme, achtsamkeitsbasierte Tätigkeiten erfasst.

Ziel der dritten Studie war es prospektiv zu untersuchen, ob und wenn ja welche, Symptom-Dimensionen der Major Depression Veränderungen der Immunparameter Il-6 und TNF-alpha über einen Monat vorhersagen. Geprüft wurde die Hypothese, dass vor allem somatische Symptome einer Major Depression einen Anstieg von pro-inflammatorischen Zytokinen voraussagen.

4. Zusammenfassungen der Studien

Im Folgenden werden die drei Studien, die im Rahmen der Dissertation durchgeführt wurden, zusammenfassend dargestellt.

4.1. Zusammenfassung Studie 1: Kindheitstraumatisierungen und kognitive Fertigkeiten bei Patienten mit Major Depression

Dannehl, K., Rief, W. & Euteneuer, F.. Childhood adversity and cognitive functioning in patients with major depression. Manuscript submitted for publication in *Child abuse and Neglect*

Hintergrund. Depression geht einher mit Symptomen von Niedergeschlagenheit, Interessenverlust oder Freudlosigkeit. Daneben zeigen sich häufig auch Beeinträchtigungen neuropsychologischer Funktionen wie Aufmerksamkeit und Gedächtnis oder veränderte exekutive Funktionen. Eine Vielzahl von Studien konnte solche veränderten neuropsychologischen Fähigkeiten bei depressiven Patienten aufzeigen, gleichzeitig zeigte sich immer wieder, dass nicht alle an Depression Erkrankten von kognitiven Einbußen betroffen sind. Diskutiert wird, ob frühe Stresserfahrungen wie Missbrauch oder Vernachlässigung spätere kognitive Fähigkeiten beeinflussen können. Die vorliegende Studie untersucht daher, ob und in welchem Ausmaß verschiedene Formen von Missbrauchserfahrungen in der Kindheit spätere neuropsychologische Veränderungen im Rahmen einer depressiven Erkrankung bedingen können.

Methode. Im Rahmen der Studie wurden 91 Patienten mit Major Depression (DSM-IV) und 40 gesunde Kontrollpersonen untersucht. Alle Probanden durchliefen eine neuropsychologische Testbatterie, welche Gedächtnis, Verarbeitungsgeschwindigkeit und exekutive Funktionen erfasste. Zudem wurde anhand des "Childhood Trauma Questionnaire" (CTQ) die Schwere und Anzahl von sexuellem, körperlichen und emotionalem Missbrauch sowie körperlicher und emotionaler Vernachlässigung erfasst. Die statistische Auswertung erfolge über hierarchische Regressionsanalysen. Dabei wurde im ersten Schritt für Probandenmerkmale (Alter, Geschlecht, Bildung) kontrolliert. In den folgenden Modellen wurden die Anzahl der Traumatisierungen und die Subskalen des CTQ als Prädiktoren eingebracht.

Ergebnisse. Zunächst zeigte sich, dass Patienten mit Major Depression im Vergleich mit der gesunden Kontrollgruppe eine signifikant höhere Anzahl an Traumatisierungen sowie schwereren emotionalen Missbrauch und emotionale/körperliche Vernachlässigung berichteten. Weiter zeigte sich, dass Patienten schlechtere Ergebnisse in Aufgaben zu verbalem Lernen (F (1, 129) = 5.01, $p < 0.05$), Allgemeinwissen (F (1, 129) = 5.00, $p < 0.05$) und Verarbeitungsgeschwindigkeit (F (1, 129) = 9.22, $p < 0.005$) zeigten als gesunde Kontrollprobanden. Die für die depressive Patientenstichprobe durchgeführten hierarchischen Regressionsanalysen ergaben zudem, dass die Anzahl der berichteten Traumatisierungen geringeres Allgemeinwissen (β = -.25, $\Delta R^2 = 0.06$, $p < 0.01$), niedrigere Verarbeitungsgeschwindigkeit (β = .22, $\Delta R^2 = 0.03$, $p < 0.05$) und eingeschränkte exekutive Funktionen vorhersagen (β = .20, $\Delta R^2 = 0.04$, $p < 0.05$). Eine Analyse der CTQ-Subskalen zeigte einen Zusammenhang zwischen körperlicher Vernachlässigung und schlechteren verbalen Lernfähigkeiten (β = -.30, $p < 0.05$) sowie zwischen körperlichem Missbrauch und reduzierten exekutiven Funktionen (β = .22, $p< 0.05$). Im Gegensatz dazu sagte die Subskala "emotionaler Missbrauch" bessere exekutive Leistungen vorher, im Sinne von mehr richtigen Antworten (β = .40, $\Delta R^2 = 0.11$, $p < 0.05$) und weniger Perseverationen (β = -0.3, $p < 0.05$) im „Modified Card Sorting Test".

Diskussion. Die Ergebnisse der Studie weisen in Übereinstimmung mit früheren Befunden darauf hin, dass Patienten mit Major Depression im Vergleich zu Gesunden neuropsychologische Einschränkungen in den Bereichen verbale Lernfähigkeiten, semantisches Gedächtnis und Verarbeitungsgeschwindigkeit aufweisen. Keine Unterschiede fanden wir bezüglich exekutiver Funktionen. Weiter zeigte sich, dass eine insgesamt höhere Anzahl an missbräuchlichen Kindheitserlebnissen niedrigere Leistungen bezüglich des semantischen Gedächtnis und der Verarbeitungsgeschwindigkeit sowie exekutiver Funktionen vorhersagte. Körperliche Vernachlässigung und körperlicher Missbrauch zeigte sich als Prädiktor für reduzierte neuropsychologische Fähigkeiten, während emotionaler Missbrauch entgegen unserer Erwartungen bessere Leistung vorhersagte. Insgesamt scheint also die Art und Menge der kindlichen Missbrauchserfahrungen unterschiedliche Auswirkungen auf kognitive Fähigkeiten im Rahmen einer depressiven Erkrankung zu haben.

4.2. Zusammenfassung Studie 2: Kognitive Verhaltenstherapie beeinflusst die Wiedererkennensleistung bei Patienten mit Major Depression

Dannehl, K., Rief, W., & Euteneuer, F.. Cognitive behavioral therapy improves recognition memory in major depression: Results of a randomized controlled trial. Manuscript submitted for publication in *Psychological Medicine.*

Hintergrund: Major Depression (MD) ist eine der häufigsten psychischen Erkrankungen der Welt (World Health Organization, 2008). Betroffene leiden nicht nur unter Störungen des Affekts und des Antriebs, sondern auch unter Defiziten im Bereich Gedächtnis und verbales Lernen. Unklar ist bisher, ob solche Defizite auch über die Remission depressiver Episoden hinaus bestehen bleiben oder sich einhergehend mit der Besserung depressiver Symptome wieder normalisieren. In der Vergangenheit zeigte sich die kognitive Verhaltenstherapie (KVT) als wirksame Therapiemethode in der Behandlung der Major Depression. Der Einfluss auf beeinträchtigte Gedächtnisfunktionen bei depressiven Patienten durch eine KVT- Behandlung ist jedoch kaum untersucht. Die bisher einzige randomisiert-kontrollierte Studie zum Einfluss von KVT auf die kognitive Leistungsfähigkeit depressiver Patienten fand keine Verbesserung auf Ebene der erfassten neuropsychologischen Parameter.

Weitere Befunde zeigen, dass Verhaltensaktivierung in Form eines Aufbaus physischer Aktivität die kognitive Leistungsfähigkeit verbessern kann. Ziel der vorliegenden Arbeit war es daher zum einen, zu untersuchen, ob KVT einen Einfluss auf Gedächtnisparameter bei depressiven Patienten haben kann. Darüber hinaus interessierte, ob die Art der Verhaltensaktivierung (regelmäßige, moderate sportlicher Betätigung versus angenehme, achtsamkeitsorientierte Betätigung), einen unterschiedlichen Effekt auf kognitive Funktionen bei Patienten mit MD ausüben kann.

Methode: Im Rahmen der Studie nahmen 98 Patienten mit MD über 16 Wochen an einer kognitiven Verhaltenstherapie teil. Zufällig zugewiesen wurden sie entweder der Bedingung KVT in Kombination mit regelmäßiger sportlicher Betätigung, KVT in Kombination mit angenehmen, achtsamkeitsbasierten Betätigungen oder einer passiven Wartekontrollgruppe (WL). Um mögliche neuropsychologische Veränderungen zum Beginn der Behandlung zu erfassen, wurden 30 gesunde, alters-gematchte Kontrollpersonen als Vergleichsgruppe hinzugezogen. Zur Erfassung der Gedächtnisfunktionen wurde der *Verbal*

Learning Memory Test zu Beginn und zum Ende der Behandlung (Woche 16) durchgeführt.

Ergebnis: Patienten mit Major Depression unterschieden sich zu Beginn der Untersuchung von gesunden Kontrollpersonen hinsichtlich ihrer kognitiven Leistungsfähigkeit in der Bereichen Lernleistung des *Verbal Learning Memory Test* (F (1, 118) = -2.9, p < 0.005), der Gesamtleistung des *Verbal Learning Memory Test* (Trial 1-5) (F (1, 118) = -2.8, p < 0.05), der Abrufleistung nach Verzögerung (F (1, 116) = -2.4, p < 0.05) und der Wiedererkennensleistung (F (1, 117) = -2.7, p < 0.01). Nach 16 Wochen Psychotherapie (KVT) zeigte sich eine klinisch relevante Remission der depressiven Symptomatik bei den Patienten der beiden KVT-Bedingungen im Vergleich zur Wartekontrollgruppe. Darüber hinaus verbesserte sich auch die Wiedererkennensleistung der Patienten der aktiven Bedingungen signifikant im Vergleich zu Wartekontrollgruppe. Keine Unterschiede zeigten sich zwischen KVT in Kombination mit regelmäßiger sportlicher Betätigung und KVT in Kombination mit angenehmen, achtsamkeitsbasierten Betätigungen.

Diskussion: Psychotherapeutische Behandlung, wie etwa kognitive Verhaltenstherapie, scheint neben einer Verbesserung des Affekts auch bestimmte Gedächtnisfunktionen beeinflussen zu können. Unsere Ergebnisse zeigen, dass Defizite in der kognitiven Leistungsfähigkeit zum Teil reversibel sind und widersprechen damit bisherigen Annahmen, welche von stabilen Defiziten in Bezug auf Gedächtnisfunktionen im Rahmen einer MD ausgehen. Frühere Untersuchungen zu Gedächtnisfunktionen zeigen, dass „freie Wiedergabe“ im Vergleich zu „Wiedererkennen“ einen aufwändigeren Prozess darstellt (Brand, Jolles, & Gispen-de Wied, 1992). Möglicherweise ist aus diesem Grund der eher passive Prozess des Wiedererkennens leichter zu verändern und reagiert sensitiver auf Veränderungen im klinischen Status der Patienten. Kognitive Prozesse, die zusätzliche Aufmerksamkeitskapazitäten und mehr Anstrengung erfordern, regenerieren sich möglicherweise deutlich langsamer.

4.3. Zusammenfassung Studie 3: Der prädiktive Wert somatischer und kognitiver depressiver Symptome in Bezug auf Veränderungen pro-inflammatorischer Zytokine bei Patienten mit Major Depression.

Dannehl, K., Rief, W., Schwarz, M., Hennings, A., Riemer, S., Selberdinger, V., Stapf, T. & Euteneuer, F. (2014). The predictive value of somatic and cognitive depressive symptoms for cytokine changes in patients with major depression. *Neuropsychiatric Disease and Treatment*, 10, 1191–1197.

Hintergrund. Die zelluläre Immunaktivierung scheint eine wichtige Rolle bei der Pathophysiologie von Depression zu spielen und vor allem eine erhöhte Konzentration von pro-inflammatorischen Zytokinen ist in der Literatur mit depressiven Symptomen assoziiert. Gleichzeitig stellt Depression an sich ein sehr heterogenes Störungsbild dar. Die aktuelle Literatur differenziert unter anderem zwischen *kognitiven* und *somatischen* Symptom-Dimensionen von Depression. Diese Symptom-Dimensionen scheinen nach aktuellen Befunden unterschiedlich mit Immunfunktionen assoziiert zu sein.

Bisher sind longitudinale Aspekte von Entzündungsparametern bei Patienten mit Major Depression wenig untersucht. Aus diesem Grund befasste sich die vorliegende Studie mit dem Einfluss verschiedener Symptom-Dimensionen von Depression auf mögliche Veränderungen der Zytokine Tumor-Nekrose-Faktor-alpha (TNF-alpha) und Interleukin-6 (IL-6) über den Verlauf von 4 Wochen. Um die Ergebnisse besser interpretieren zu können, wurde zusätzlich die grundlegende Stabilität dieser Zytokine erfasst.

Methode. Im Rahmen der Studie wurden 41 Patienten mit Major Depression und 45 gesunde Kontrollpersonen untersucht. Um einen Zusammenhang zwischen kognitiv-affektiven und somatischen Symptomen der MD und Veränderungen der pro-inflammatorischen Zytokine TNF-alpha und IL-6 zu erfassen, wurden hierarchische Regressionsanalysen durchgeführt. Die Baseline-Spiegel der Zytokine wurden hierbei in Schritt 1 eingefügt, die Symptom-Dimensionen in Schritt 2. Mittels Moderationsanalysen wurde eine mögliche Interaktion zwischen Geschlecht und Symptom-Dimensionen erfasst. Exploratorische Analysen der Intra-Class-Koeffizienten wurden zusätzlich betrachtet, um Aussagen über die grundlegende Stabilität der Immunparameter treffen zu können. Die psychometrischen Messungen beinhalteten sowohl die Erfassung kognitiv-affektiver de-

pressiver Symptome als auch somatischer Symptome der letzten 7 Tage wie auch der letzten 2 Jahre mittels des Screenings für somatoforme Störungen (SOMS-7 und SOMS-2).

Ergebnisse. Patienten mit Depression zeigten erhöhte Level von TNF-alpha (F (1, 87) = 0.16, p = 0.045) im Vergleich zu gesunden Kontrollpersonen. Keine Gruppenunterschiede fanden sich dagegen für Il-6. Zusätzliche hierarchische Regressionsanalysen zeigten, dass weder kognitiv-affektive noch somatische Symptome Veränderungen von proinflammatorischen Zytokinen bei depressiven Patienten vorhersagen (p > 0.1). Weitergehende Moderationsanalysen zeigten, dass die Interaktion SOMS-2 X Geschlecht einen signifikanten Varianzanteil der Veränderungen von TNF-alpha erklärt (β = -.40, ΔR^2= 0.046, p = .027). Nachfolgende, nach Geschlecht stratifizierte Regressionsanalysen zeigten, dass somatische Symptome während der letzten 2 Jahre einen signifikanten Anstieg von TNF-alpha bei Frauen mit MD (β = .31, p = .019, ΔR^2= 0.095), nicht aber bei Männern vorhersagen (β = -.01, ΔR^2< 0.001, p = .930). Dagegen sind weder somatische Symptome während der letzten 7 Tage (p = .557, ΔR2= 0.003, β = .06) noch kognitiv-affektive depressive Symptome (β = .15, ΔR2= 0.021, p = .124) signifikante Prädiktoren immunologischer Veränderungen. Die via Intra-Class-Koeffizienten erfasste Stabilität der Zytokine zeigte sich hoch für TNF-alpha und moderat für Il-6.

Diskussion. Die Ergebnisse der Studie liefern weitere Evidenz für eine erhöhte Zytokinkonzentration (TNF-alpha) bei Patienten mit MD. Zudem konnte die Bedeutung der Differenzierung zwischen somatischen und kognitiv-affektiven Merkmalen innerhalb des Störungsbildes Depression gefestigt werden. So zeigte sich, dass langanhaltende somatische, nicht aber kognitiv-affektive depressive Symptome, einen Anstieg von TNF-alpha bei Frauen mit Major Depression vorhersagen. Die Ergebnisse weisen zudem auf psychoneuroimmunologische Geschlechtsunterschiede im Zusammenhang mit Depression hin. Für die klinische Praxis erscheint es wichtig, vor allem somatische Aspekte einer depressiven Erkrankung im Hinblick auf den weiteren Erkrankungsverlauf wie auch auf körperliche Erkrankungen ernst zu nehmen und entsprechende therapeutische Implikationen abzuleiten.

5. Limitationen

Bei der Interpretation der Ergebnisse sind einige Einschränkungen zu berücksichtigen. Bei allen drei Studien bestand eine relativ hohe Selektivität der Stichprobe: Alle teilnehmenden Patienten wurden in der Ambulanz für Psychotherapie Marburg rekrutiert und bildeten somit eine therapiemotivierte, ambulant behandelbare Stichprobe. Die Ergebnisse der vorliegenden Arbeit lassen sich daher nicht unbedingt auf eine repräsentative Stichprobe, welche beispielsweise auch Patienten mit psychotischen Merkmalen beinhaltet, generalisieren.

Zu den methodischen Einschränkungen zählt der Einsatz von retrospektiven Fragebögen zur Erfassung der Kindheitstraumatisierungen in Studie I. Auch wenn der verwendete *Childhood Trauma Questionnaire* (CTQ) sich als stabiles Messinstrument erwiesen hat (Hardt & Rutter, 2004; Lizardi & Klein, 2005; Paivio, 2001), ist nicht gänzlich auszuschließen, dass bedingt durch die vorliegende depressive Erkrankung und damit einhergehender möglicher negativer Sicht auf die Vergangenheit, eine Überschätzung negativer Kindheitserlebnisse stattgefunden hat. Zudem wurde zwar eine mögliche PTBS-Diagnose (SKID-I) erfasst, nicht aber systematisch für erst im Erwachsenenalter aufgetretene belastende Ereignisse kontrolliert. Es ist nicht auszuschließen, dass massiver Stress im Erwachsenenalter ebenfalls kognitive Einbußen mit bedingt haben mag. Zudem ist für Studie I kritisch anzumerken, dass das kognitive Funktionsniveau nur im Querschnitt erhoben wurde, was kausale Interpretationen nicht zulässt.

In Studie II wurde die Menge an körperlicher Aktivität per Selbstberichtsmaß erfasst. Der hierzu von uns genutzte *International Physical Activity Questionnaire* (IPAQ) weist zwar eine gute Reliabilität und Validität auf (Craig et al., 2003; Wanner et al., 2016), es ist jedoch nicht auszuschließen, dass die Probanden ihre tatsächliche Aktivität sozial erwünscht berichtet haben. Weiter ist für Studie II kritisch anzumerken, dass beide KVT-Bedingungen mit einer Komponente der Verhaltensaktivierung kombiniert waren (Bewegung vs. Angenehme, achtsamkeitsbasierte Aktivität). Das Studiendesign lässt somit keine Aussagen darüber zu, ob Verhaltensaktivierung, kognitive Interventionen oder die Kombination aus beidem die berichtete Verbesserung der Wiedererkennensleistung bedingt haben.

Weiter kritisch zu betrachten ist die in Studie III relativ kleine Stichprobengröße (41 Patienten mit MD). Auch in Studie II ist trotz einer zufriedenstellenden Gesamtstichprobengröße von 98 Patienten mit MD die Anzahl der Probanden in den einzelnen Inter-

ventionsbedingungen recht klein. Eine Replikation der Ergebnisse mit größerer Stichprobenzahl wäre hier sicher wünschenswert.

6. Implikationen für Forschung und Praxis

Im Hinblick auf die große Anzahl Betroffener scheint weitere differenzierte Forschung bezüglich der Pathogenese der Major Depression und diese moderierende Faktoren unabdingbar. Eine Verfeinerung der Diagnostik sowie die Entwicklung individueller Behandlungsansätze sind von großer Relevanz.

In Studie I konnte ein möglicher Zusammenhang von frühkindlichem, massivem Stress und späteren eingeschränkten Gedächtnisfunktionen aufgezeigt werden. Um diese Befunde zu bestätigen und vermittelnde Mechanismen dieses Zusammenhangs weiter zu spezifizieren, sind insbesondere prospektive Langzeitstudien notwendig. Solche müssten Kinder in Bezug auf neurobiologische Veränderungen, psychosoziale Umgebungsfaktoren und spätere mögliche psychische Erkrankungen begleiten, um detaillierte Informationen über mögliche Zusammenhänge von Stresserfahrungen und späteren Einschränkungen zu erhalten und mögliche weitere Moderatoren dieses Zusammenhangs zu identifizieren. Auch die Erfassung von möglichen Resilienzfaktoren scheint hierbei von großem Interesse, da nicht alle Kinder, welche körperlichem oder emotionalem Missbrauch ausgesetzt sind, psychische Probleme oder neuropsychologische Defizite entwickeln (Chen & Miller, 2012).

Die in der vorliegenden Arbeit (Studie II) gefundenen Ergebnisse liefern erste Hinweise darauf, dass KVT in Kombination mit Verhaltensaktivierung in Form von Bewegung oder achtsamkeitsorientierten Tätigkeiten positive Effekte sowohl auf depressive Symptome wie auch auf mnestische Beeinträchtigungen haben kann. Im Vergleich zur Wartekontrollgruppe zeigten beide KVT Bedingungen nach 16 Stunden KVT eine Verbesserung der Wiedererkennensleistung. Da unklar ist, ob kognitive Interventionen, Verhaltensaktivierung oder die Kombination aus beidem für die Effekte verantwortlich ist, gilt es, in zukünftigen Studien die einzelnen Komponenten weiter zu untersuchen und konkrete Wirkmechanismen zu erfassen.

Aktuelle eigene Arbeiten zeigen einen Anstieg des anti-inflammatorischen Zytokins Interleukin (IL)-10 durch KVT mit Bewegungsaufbau sowie eine Reduktion des CRP-Spiegels bei Patienten mit erhöhtem kardiovaskulären Risiko (definiert durch erhöhte Konzentrationen des Entzündungsmarkers CRP) (Euteneuer et al., 2017). Eine aktuelle Arbeit von Monteiro und Kollegen liefert zudem vielversprechende erste Hinweise auf einen positiven Effekt von anti-inflammatorischer Behandlung auf Gedächtnisfunktionen (Monteiro et al., 2016). Inwieweit eine anti-inflammatorische Wirkung durch physische

Aktivität im Rahmen der KVT bei Depression langfristig auch positive Effekte auf mnestische Funktionen haben mag, sollte zukünftig weiter untersucht werden.

Studie III der vorliegenden Arbeit lässt vermuten, dass vor allem Patienten mit einem eher „somatischen" depressiven Symptombild immunologische Veränderungen aufweisen (Dannehl et al., 2014). Depressive Patienten, welche erhöhte Entzündungsparameter zeigen, scheinen zudem mit mehr medizinischen Komorbiditäten, einem erhöhten Body Mass Index sowie einer schlechteren Behandlungsprognose konfrontiert zu sein (Gallagher et al., 2016). Eine Differenzierung der Symptome depressiver Patienten hinsichtlich eines kognitiv-affektiven versus somatisches Profil, wie wir dies in der vorliegenden Arbeit (Studie III) getan haben, scheint daher höchst sinnvoll und könnte zukünftige Behandlungsansätze individualisieren. Gegenstand zukünftiger Forschung sollte die weitere Untersuchung von immunologischen Auffälligkeiten und mit diesen assoziierten ätiologischen und klinischen Charakteristika der Depression sein, um Subtypen und individuelle Interventionen für diese weiter spezifizieren zu können.

Die Integration dieser Forschungsergebnisse in die klinische Praxis stellt eine Herausforderung dar. Aus klinischer Perspektive erscheint vor allem die Weiterentwicklung und Implementierung von präventiven Interventionen, welche Gewalt gegen Kinder verhindern helfen, höchst relevant (Gershoff, Lee, & Durrant, 2017). Unterstützungsangebote für Familien und Beratungsangebote spielen hierbei eine wichtige Rolle und sollten weiter evaluiert werden (Coore Desai, Reece, & Shakespeare-Pellington, 2017). Zudem gilt es bei Bedarf, frühzeitig notwendige psychotherapeutische Interventionen einzuleiten, um so psychischen Störungen und deren Chronifizierung im Erwachsenenalter präventiv zu begegnen. Weiter scheint es von Relevanz, in der Behandlung depressiver Patienten mögliche frühe Stresserfahrungen diagnostisch zu erfassen und Interventionen, Dauer und Intensität der Behandlung entsprechend anzupassen. Ein Behandlungsansatz, der missbräuchliche Erfahrungen in der Entwicklung eine Major Depression besonders in den Blick nimmt, ist die *Cognitive Analysis System of Psychotherapy* (CBASP), entwickelt für chronisch depressive Patienten (McCullough, 2003). In einer Studie von Nemeroff und Kollegen erwies sich CBASP insbesondere bei depressiven Patienten mit frühen Traumatisierungen als erfolgreich (Nemeroff et al., 2003). Ergebnisse aus unserer eigenen Arbeitsgruppe fanden bislang keine signifikante Überlegenheit von CBASP im Vergleich zu einer 16-stündigen KVT-Behandlung (Rief, Bleichhardt, Dannehl, Euteneuer, & Wambach, 2017). Weitere Untersuchungen hinsichtlich der Wirksamkeit neuer psychotherapeutischer Behandlungsansätze, wie etwa CBASP, scheinen hier noch notwendig.

Bezüglich neuropsychologischer Einschränkungen, welche im Rahmen einer MD auftreten und maßgeblich das Funktionsniveau (z.B. Lebensqualität, Arbeitsfähigkeit, Alltagsbewältigung) innerhalb einer MD beeinflussen können (Bortolato et al., 2014), scheint es von Bedeutung, diese bei der Behandlung der Depression gezielt in den Blick zu nehmen. Oertel-Knöchel und Kollegen zeigten, dass eine Steigerung des Bewegungsverhaltens in Kombination mit gezielten kognitiven Trainingskomponenten gute Behandlungserfolge in Bezug auf kognitive Einschränkungen bei Patienten mit MD bieten kann (Knöchel et al., 2012). Bowie und Kollegen fanden bei einem 10-wöchigen Online-Training zur Förderung kognitiver Fähigkeiten positive Effekte auf die kognitive Leistungsfähigkeit in einer Gruppe bis dahin behandlungsresistenter depressiver Patienten (Bowie et al., 2013). Auch neuere psychotherapeutische Ansätze wie etwa die Metakognitive Therapie, welche Aufmerksamkeitsprozesse beeinflussen kann, bieten möglicherweise ebenfalls einen hilfreichen Behandlungsansatz für Patienten mit kognitiven Einschränkungen und bedürfen weiterer Forschung (Groves et al., 2015; Wells et al., 2009). Risikofaktoren für neuropsychologische Defizite scheinen zudem Einsamkeit und Langeweile zu sein (Conroy, Golden, Jeffares, O´Neill, & McGee, 2010). Der Aufbau verhaltensaktivierender Interventionen -wie sie auch in der vorliegenden Arbeit in Studie II beschrieben werden- scheinen aufgrund dessen nicht nur im Hinblick auf eine Reduktion der depressiven Symptomatik sondern auch hinsichtlich neuropsychologischer Defizite essentielle Behandlungsziele zu sein (Cuijpers et al., 2014).

Auch die Subgruppe depressiver Patienten mit erhöhten Entzündungsparametern gilt es in Zukunft weiter gezielt zu untersuchen. Es stellt sich die Frage, ob und bei welchen Patientengruppen Ansätze, die vor allem eine anti-entzündliche Wirkung haben, greifen können. Bisher scheinen etwa TNF-alpha-Antagonisten, wie Etanercept oder Infliximab, zumindest teilweise wirksam in der Behandlung der MD zu sein (Raison et al., 2013; Tyring et al., 2006). Auch in Bezug auf nicht medikamentöse anti-entzündliche Behandlungsansätze, wie beispielsweise eine Veränderung der Ernährung oder des Bewegungsverhaltens, gilt es die bisherige noch geringe Datenlage auszubauen (Esposito et al., 2004; Kasapis & Thompson, 2005; Milanschi et al., 2011) und mögliche Einflussmöglichkeiten auf Entzündungsprozesse weiter zu eruieren. Erste Ergebnisse eigener Arbeiten weisen auf eine anti-inflammatorische Wirkung physischer Aktivität im Rahmen einer kognitiven Verhaltenstherapie bei Depression hin (Euteneuer et al., 2017). Neben medikamentösen und Verhaltens-ändernden Interventionen bieten gegebenenfalls auch stressreduzierende

Verfahren wie beispielsweise Tai Chi oder Yoga (Lavretsky et al., 2011; Sengupta, 2012) sinnvolle, Entzündungsparameter beeinflussende Behandlungsansätze.

7. Fazit

Die hier vorliegende kumulative Dissertation liefert Hinweise für die Relevanz frühkindlicher massiver Stresserfahrungen bei der Entstehung von kognitiven Defiziten im Rahmen einer Major Depression. Darüber hinaus zeigt die Arbeit, dass kognitive Defizite zumindest teilweise reversibel sein können und die kognitive Verhaltenstherapie hierbei einen wirksamen Behandlungsansatz bietet. Daneben konnte dargestellt werden, dass eine Major Depression immunologische Veränderungen bedingt und eine differenzierte Betrachtung depressiver Symptome einhergehend mit einer Unterscheidung von Symptom-Dimensionen sinnvoll ist.

8. Literatur

Aas, M., Steen, N. E., Agartz, I., Aminoff, S. R., Lorentzen, S., Sundet, K., & Melle, I. (2012). Is cognitive impairment following early life stress in severe mental disorders based on specific or general cognitive functioning? *Psychiatry Research*, *198*(3), 495–500. doi.org/10.1016/j.psychres.2011.12.045

Bastos, A. G., Pinto Guimarães, L. S., & Trentini, C. M. (2013). Neurocognitive changes in depressed patients in psychodynamic psychotherapy, therapy with fluoxetine and combination therapy. *Journal of Affective Disorders*, *151*(3), 1066–1075. doi.org/10.1016/j.jad.2013.08.036

Beckmann Bosaipo, N., Paula, M., Young, A. H., & Francisco, M. (2017). Neuroscience and Biobehavioral Reviews Neuropsychological changes in melancholic and atypical depression : A systematic review. *Neuroscience and Biobehavioral Reviews*, *73*, 309–325. doi.org/10.1016/j.neubiorev.2016.12.014

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., … Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry*, *151*(8), 1132–6. doi.org/10.1176/ajp.151.8.1132

Biringer, E., Mykletun, A., Sundet, K., Kroken, R., Stordal, K. I., & Lund, A. (2007). A longitudinal analysis of neurocognitive function in unipolar depression. *Journal of Clinical and Experimental Neuropsychology*, *29*(8), 879–91. doi.org/10.1080/13803390601147686

Bortolato, B., Carvalho, A. F., & McIntyre, R. S. (2014). Cognitive Dysfunction in Major Depressive Disorder: A State-of-the-Art Clinical Review. *CNS & Neurological Disorders-Drug Targets*, *13*(10), 1804–1818. doi.org/10.2174/1871527313666141130203823

Bosch, N. M., Riese, H., Dietrich, A., Ormel, J., Verhulst, F. C., & Oldehinkel, A. J. (2009). Preadolescents' Somatic and Cognitive-Affective Depressive Symptoms Are Differentially Related to Cardiac Autonomic Function and Cortisol: The TRAILS Study. *Psychosomatic Medicine*, *950*, 944–950. doi.org/10.1097/PSY.0b013e3181bc756b

Bowie, C. R., Gupta, M., Holshausen, K., Jokic, R., Best, M., & Milev, R. (2013). Cognitive Remediation for Treatment-Resistant Depression. *The Journal of Nervous and Mental Disease*, *201*(March), 680–685.

doi.org/10.1097/NMD.0b013e31829c5030

Brakemeier, E.-L., Schramm, E., & Hautzinger, M. (2012). *Chronische Depression (Fortschritte der Psychotherapie)* (1st ed.). Hogrefe.

Brand, A. N., Jolles, J., & Gispen-de Wied, C. (1992). Recall and recognition memory deficits in depression. *Journal of Affective Disorders*, *25*(1), 77–86. doi.org/10.1016/0165-0327(92)90095-N

Brand, M., & Markowitsch, H. J. (2004). Neurocognition of Psychiatric Patients. *Psychiatry Praxis*, *31*, 200–209. doi.org/10.1055/s-2004-828481

Bull, S. J., Huezo-Diaz, P., Binder, E. B., Cubells, J. F., Ranjith, G., Maddock, C., … Pariante, C. M. (2009). Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-α and ribavirin treatment. *Molecular Psychiatry*, *14*(12), 1095–1104. doi.org/10.1038/mp.2008.48

Busch, M. A., Maske, U. E., Ryl, L., Schlack, R., & Hapke, U. (2013). Prävalenz von depressiver Symptomatik und diagnostizierter Depression bei Erwachsenen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz*, *56*(5-6), 733–739. doi.org/10.1007/s00103-013-1688-3

Carmichael, M. D., Davis, J. M., Murphy, E. A., Brown, A. S., Carson, J. A., Mayer, E. P., & Ghaffar, A. (2006). Role of brain IL-1beta on fatigue after exercise-induced muscle damage. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *291*(5), R1344–8. doi.org/10.1152/ajpregu.00141.2006

Carpenter, L. L., Shattuck, T. T., & Price, L. H. (2011). Effect of childhood physical abuse on cortisol stress response. *Psychoneuroendocrinology*, *214*(1), 367–375. doi.org/10.1007/s00213-010-2007-4.Effect

Carrion, Victor G, Weems, C. F., Richert, K., Hoffmann, B. C., & Reiss, A. L. (2010). Decreased Prefrontal Cortical Volume Associated With Increased Bedtime Cortisol in Traumatized Youth. *Biological Psychiatry*, *68*(5), 491–493. doi.org/10.1016/j.biopsych.2010.05.010.Decreased

Carrion, V. G., Weems, C. F., & Reiss, A. L. (2007). Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. *Pediatrics*, *119*(3), 509–16. doi.org/10.1542/peds.2006-2028

Chamberlain, S. R., & Sakakian, B. J. (2006). The neuropsychology of mood disorders. *Current Psychiatry Reports*, *8*(6), 458–463. doi.org/10.1007/s11920-006-0051-x

Chang, Y.-K., Labban, J., Gapin, J., & Etnier, J. L. (2012). The effects of acute exercise on

cognitive performance: A meta-analysis. *Brain Research*, *1470*, 1–15. doi.org/10.1016/j.brainres.2012.06.039

Chen, E., & Miller, G. E. (2012). Shift-and-Persist" Strategies: Why Being Low in Socioeconomic Status isn't Always Bad for Health. *Perspectives in Psychological Science*, *7*(2), 135–158. doi.org/10.1177/1745691612436694.

Cloitre, M., Stovall-McClough, C., Zorbas, P., & Charuvastra, A. (2008). Attachment Organization, Emotion Regulation, and Expectations of Support in a Clinical Sample of Women With Childhood Abuse Histories. *Journal of Traumatic Stress*, *21*(3), 282–289. doi.org/10.1002/jts.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults. *Psychological Science*, *14*, 125. doi.org/10.1111/1467-9280.t01-1-01430

Conroy, R. M., Golden, J., Jeffares, I., O´Neill, D., & McGee, H. (2010). Boredom-proneness, loneliness, social engagement and depression and their association with cognitive function in older people: a population study. *Psychology, Health and Medicine*, *15*(4), 463–473. doi.org/10.1080/13548506.2010.487103

Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., … Mead, G. E. (2013). Exercise for depression. *The Cochrane Database of Systematic Reviews*, *9*, CD004366. doi.org/10.1002/14651858.CD004366.pub6

Coore Desai, C., Reece, J.-A., & Shakespeare-Pellington, S. (2017). The prevention of violence in childhood through parenting programmes: a global review. *Psychology, Health & Medicine*, *8506*(February), 1–21. doi.org/10.1080/13548506.2016.1271952

Copeland, W. E., Shanahan, L., Worthman, C., Angold, A., & Costello, E. J. (2013). Cumulative Depression Episodes Predicts Later C-Reactive Protein Levels: A Prospective Analysis William. *Biological Psychiatry*, *71*(1), 15–21. doi.org/10.1016/j.biopsych.2011.09.023.Cumulative

Cotrena, C., Branco, L. D., Shansis, F. M., & Fonseca, R. P. (2016). Executive function impairments in depression and bipolar disorder: Association with functional impairment and quality of life. *Journal of Affective Disorders*, *190*, 744–753. doi.org/10.1016/j.jad.2015.11.007

Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., … Oja, P. (2003). International physical activity questionnaire: 12-Country reliability and validity. *Medicine and Science in Sports and Exercise*, *35*(8), 1381–1395. doi.org/10.1249/01.MSS.0000078924.61453.FB

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S.

(2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, *58*(7), 376–85.

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S. D., & Van Straten, A. (2014). The effects of psychotherapies for major depression in adults on remission, recovery and improvement: A meta-analysis. *Journal of Affective Disorders*, *159*, 118–126. doi.org/10.1016/j.jad.2014.02.026

Danese, A., Moffitt, T. E., Harrington, H., Milne, B. J., Polanczyk, G., Pariante, C. M., … Caspi, A. (2013). Adverse Childhood Experiences and Adult Risk Factors for Age-Related Disease: Depression, Inflammation, and Clustering of Metabolic Risk Markers. *Archives of Pediatrics and Adolescent Medicine*, *163*(12), 1135–1143. doi.org/10.1001/archpediatrics.2009.214.

Dannehl, K., Rief, W., Schwarz, M. J., Hennings, A., Riemer, S., Selberdinger, V.,Stapf, T. Euteneuer, F. (2014). The predictive value of somatic and cognitive depressive symptoms for cytokine changes in patients with major depression. *Neuropsychiatric Disease and Treatment*, *10*, 1191–1197. doi.org/10.2147/NDT.S61640

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews. Neuroscience*, *9*(1), 46–56. doi.org/10.1038/nrn2297

Deuschle, M., Kniest, A., Niemann, H., Erb-Bies, N., Colla, M., Hamann, B., & Heuser, I. (2004). Impaired declarative memory in depressed patients is slow to recover: Clinical experience. *Pharmacopsychiatry*, *37*(4), 147–151. doi.org/10.1055/s-2004-827168

Deverts, D., Cohen, S., DiLillo, V. G., Lewis, C. E., Kiefe, C., Whooley, M., & Matthews, K. A. (2011). Depressive Symptoms, Race, and Circulating C-Reactive Protein: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Psychosomatic Medicine*, *72*(8), 734–741. doi.org/10.1097/PSY.0b013e3181ec4b98.Depressive

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., Addis, M. E., … Jacobson, N. S. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology*, *74*(4), 658–70. doi.org/10.1037/0022-006X.74.4.658

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K.

L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67*(5), 446–57. doi.org/10.1016/j.biopsych.2009.09.033

Duivis, H. E., Vogelzangs, N., Kupper, N., de Jonge, P., & Penninx, B. W. J. H. (2013). Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology*, *38*(9), 1573–85. doi.org/10.1016/j.psyneuen.2013.01.002

Dunkin, J. J., Leuchter, A. F., Cook, I. A., Kasl-Godley, J. E., Abrams, M., & Rosenberg-Thompson, S. (2000). Executive dysfunction predicts nonresponse to fluoxetine in major depression. *Journal of Affective Disorders*, *60*(1), 13–23. doi.org/10.1016/S0165-0327(99)00157-3

Egeland, J., Sundet, K., Rund, B. R., Asbjørnsen, A., Hugdahl, K., Landrø, N. I., … Stordal, K. I. (2003). Sensitivity and specificity of memory dysfunction in schizophrenia: a comparison with major depression. *Journal of Clinical and Experimental Neuropsychology*, *25*(1), 79–93. doi.org/10.1076/jcen.25.1.79.13630

Esposito, K., Marfella, R., Ciotola, M., Di Palo, C., Giugliano, F., Giugliano, G., … Giugliano, D. (2004). Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome - A randomized trial. *Journal of the American Medical Association*, *292*(12), 1440–1446. doi.org/10.1001/jama.292.12.1440

Euteneuer, F., Dannehl, K., del Rey, A., Engler, H., Schedlowski, M., & Rief, W. (2017). Immunological effects of behavioral activation with exercise in major depression: An exploratory randomized controlled trial. *Accepted for Publication in Translational Psychiatry*.

Euteneuer, F., Schwarz, M. J., Dannehl, K., Hartung, A., Westermann, S., & Rief, W. (2012). Increased soluble interleukin-2 receptor levels are related to somatic but not to cognitive-affective features in major depression. *Brain, Behavior, and Immunity*, *26*(8), 1244–8. doi.org/10.1016/j.bbi.2012.06.007

Gallagher, D., Kiss, A., Lanctot, K., & Herrmann, N. (2016). Depression with inflammation: longitudinal analysis of a proposed depressive subtype in community dwelling older adults. *Internation Journal of Geriatric Psychiatry*. doi.org/10.1002/gps.4645

Gershoff, E. T., Lee, S. J., & Durrant, J. E. (2017). Promising intervention strategies to reduce parents' use of physical punishment. *Child Abuse & Neglect*, 1–15.

doi.org/10.1016/j.chiabu.2017.01.017

Gili, M., Roca, M., Armengol, S., Asensio, D., Garcia-Campayo, J., & Parker, G. (2012). Clinical patterns and treatment outcome in patients with melancholic, atypical and non-melancholic depressions. *PloS One*, *7*(10), e48200. doi.org/10.1371/journal.pone.0048200

Gillespie, C. F., & Nemeroff, C. B. (2005). Early Life Stress and Depression. Childhood trauma may lead to neurobiologically unique mood disorders. *Current Psychiatry*, *4*(10).

Gould, F., Clarke, J., Heim, C., Harvey, P. D., Majer, M., & Nemeroff, C. B. (2012). The effects of child abuse and neglect on cognitive functioning in adulthood. *Journal of Psychiatric Research*, *46*(4), 500–6. doi.org/10.1016/j.jpsychires.2012.01.005

Grant, M. M., Thase, M. E., & Sweeney, J. A. (2001). Cognitive disturbance in outpatient depressed younger adults: Evidence of modest impairment. *Biological Psychiatry*, *50*(1), 35–43. doi.org/10.1016/S0006-3223(00)01072-6

Grassi-Oliveira, R., Bauer, M. E., Pezzi, J. C., Teixeira, A. L., & Brietzke, E. (2011). Interleukin-6 and verbal memory in recurrent major depressive disorder. *Neuro Endocrinology Letters*, *32*(4), 540–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21876502

Grobe, T. G., & Steinmann, S. (2015). Depressionsatlas -Auswertungen zu Arbeitsunfähigkeit und Arzneiverordnungen. *Göttingen: Techniker Krankenkasse*.

Groves, S. J., Porter, R. J., Jordan, J., Knight, R., Carter, J. D., McIntosh, V. V. W., Joyce, P. R. (2015). Changes in neuropsychological function after treatment with metacognitive therapy or cognitive behavior therapy for depression. *Depression and Anxiety*, *32*(6), 437–444. doi.org/10.1002/da.22341

Gualtieri, C. T., & Morgan, D. W. (2008). The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *The Journal of Clinical Psychiatry*, *69*(7), 1122–30.

Hadianfard, H. (2014). Child abuse in group of children with attention deficit-hyperactivity disorder in comparison with normal children. *International Journal of Community Based Nursing and Midwifery*, *2*(2), 77–84. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4201192&tool=pmcentrez&rendertype=abstract

Halvorsen, M., Waterloo, K., Sundet, K., Eisemann, M., & Wang, C. E. A. (2011). Verbal learning and memory in depression: A 9-year follow-up study. *Psychiatry Research*,

188(3), 350–354. doi.org/10.1016/j.psychres.2011.02.022

Hammar, A., & Ardal, G. (2009). Cognitive functioning in major depression--a summary. *Frontiers in Human Neuroscience*, *3*(September), 26. doi.org/10.3389/neuro.09.026.2009

Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of Child Psychology and Psychiatry*, *45*(2), 260–273. doi.org/10.1111/j.1469-7610.2004.00218.x

Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: A systematic review. *Journal of Affective Disorders*, *134*(1-3), 20–31. doi.org/10.1016/j.jad.2010.11.011

Hautzinger, M. (2013). *Kognitive Verhaltenstherapie bei Depressionen* (7th ed.). Beltz.

Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., … Nemeroff, C. B. (2000). Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood. *The Journal of the American Medical Association*, *284*(5), 3–8. doi.org/10.1001/jama.284.5.592

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*, *33*(6), 693–710. doi.org/10.1016/j.psyneuen.2008.03.008

Herrera-Guzmán, I., Gudayol-Ferré, E., Herrera-Guzmán, D., Guàrdia-Olmos, J., Hinojosa-Calvo, E., & Herrera-Abarca, J. E. (2009). Effects of selective serotonin reuptake and dual serotonergic-noradrenergic reuptake treatments on memory and mental processing speed in patients with major depressive disorder. *Journal of Psychiatric Research*, *43*(9), 855–863. doi.org/10.1016/j.jpsychires.2008.10.015

Jokela, M., Virtanen, M., Batty, G. D., & Kivimäki, M. (2016). Inflammation and Specific Symptoms of Depression. *JAMA Psychiatry*, *73*(1), 1–6. doi.org/10.1001/jamapsychiatry.2015.1977.Author

Jonge, P. De, Mangano, D., & Whooley, M. A. (2007). Differential association of cognitive and somatic depressive symptoms with heart reate variability in patients with stable coronary heart disease: findings from the heart and soul study. *Psychosomatic Medicine*, *69*(8), 735–739. doi.org/10.1097/PSY.0b013e31815743ca.Differential

Kasapis, C., & Thompson, P. D. (2005). The effects of physical activity on serum C-reactive protein and inflammatory markers: A systematic review. *Journal of the American College of Cardiology*, *45*(10), 1563–1569.

doi.org/10.1016/j.jacc.2004.12.077

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. a, Zaslavsky, A. M., … Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *The British Journal of Psychiatry : The Journal of Mental Science*, *197*(5), 378–85. doi.org/10.1192/bjp.bp.110.080499

Kiecolt-Glaser, J. K., Derry, H. M., & Fagundes, C. P. (2015). Inflammation: Depression fans the flames and feasts on the heat. *American Journal of Psychiatry*, *172*(11), 1075–1091. doi.org/10.1176/appi.ajp.2015.15020152

Klein, D. N., Ph, D., Arnow, B. A., Barkin, J. L., Dowling, F., Kocsis, J. H., Wisniewski, S. R. (2009). Early Adversity in Chronic Depression: Cinical Correlates and Response to Pharmacotherapy. *Depression and Anxiety*, *26*, 701–710. doi.org/10.1002/da.20577.

Knöchel, C., Oertel-Knöchel, V., O'Dwyer, L., Prvulovic, D., Alves, G., Kollmann, B., & Hampel, H. (2012). Cognitive and behavioural effects of physical exercise in psychiatric patients. *Progress in Neurobiology*, *96*(1), 46–68. doi.org/10.1016/j.pneurobio.2011.11.007

Köhler, C., Freitas, T., Maes, M., de Andrade, N., Liu, C., Fernandes, B., … Carvalho, A. F. (2017). Peripheral cytokine and chemokine alterations in depression:a meta-analysis of 82 studies. *Acta Psychiatrica Scandinavica*, 1–15. doi.org/10.1111/acps.12698

Köhler, O., Benros, M. E., Nordentoft, M., Farkouh, M. E., Iyengar, R. L., Mors, O., & Krogh, J. (2014). Effect of Anti-inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects. *JAMA Psychiatry*, *71*(12), 1381. doi.org/10.1001/jamapsychiatry.2014.1611

Korten, N. C. M., Comijs, H. C., Lamers, F., & Penninx, B. W. J. H. (2012). Early and late onset depression in young and middle aged adults: differential symptomatology, characteristics and risk factors? *Journal of Affective Disorders*, *138*(3), 259–67. doi.org/10.1016/j.jad.2012.01.042

Kupper, N., Widdershoven, J. W., & Pedersen, S. S. (2012). Cognitive/affective and somatic/affective symptom dimensions of depression are associated with current and future inflammation in heart failure patients. *Journal of Affective Disorders*, *136*(3), 567–76. doi.org/10.1016/j.jad.2011.10.029

Lamers, F., de Jonge, P., Nolen, W. a, Smit, J. H., Zitman, F. G., Beekman, A. T. F., & Penninx, B. W. J. H. (2010). Identifying depressive subtypes in a large cohort study:

results from the Netherlands Study of Depression and Anxiety (NESDA). *The Journal of Clinical Psychiatry*, *71*(12), 1582–9. doi.org/10.4088/JCP.09m05398blu

Lavretsky, H., Alstein, L. L., Olmstead, R. E., Ercoli, L. M., Riparetti-Brown, M., Cyr, N. S., & Irwin, M. R. (2011). Complementary use of tai chi chih augments escitalopram treatment of geriatric depression: a randomized controlled trial. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*, *19*(10), 839–50. doi.org/10.1097/JGP.0b013e31820ee9ef

Lee, R. S. C., Hermens, D. F., Porter, M. a, & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of Affective Disorders*, *140*(2), 113–24. doi.org/10.1016/j.jad.2011.10.023

Lin, K., Xu, G., Lu, W., Ouyang, H., Dang, Y., Lorenzo-Seva, U., … Lee, T. M. C. (2014). Neuropsychological performance in melancholic, atypical and undifferentiated major depression during depressed and remitted states: A prospective longitudinal study. *Journal of Affective Disorders*, *168*, 184–191. doi.org/10.1016/j.jad.2014.06.032

Lindert, J., von Ehrenstein, O. S., Grashow, R., Gal, G., Braehler, E., & Weisskopf, M. G. (2013). Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: systematic review and meta-analysis. *International Journal of Public Health*, 359–372. doi.org/10.1007/s00038-013-0519-5

Linke, S. E., Rutledge, T., Johnson, B. D., Vaccarino, V., Bittner, V., Cornell, C. E., … Bairey, C. N. (2009). Depressive Symptom Dimensions and Cardiovascular Prognosis among Women with Suspected Myocardial Ischemia: A Report from the NHLBI-Sponsored WISE Study. *Archives of General Psychiatry*, *66*(5), 499–507. doi.org/10.1001/archgenpsychiatry.2009.27.

Lizardi, H., & Klein, D. N. (2005). Long-Term Stability of Parental Representations in Depressed Outpatients Utilizing the Parental Bonding Instrument. *The Journal of Nervous and Mental Disease*, *193*(3), 183–188. doi.org/10.1097/01.nmd.0000154838.16100.36

Majer, M., Nater, U. M., Lin, J.-M. S., Capuron, L., & Reeves, W. C. (2010). Association of childhood trauma with cognitive function in healthy adults: a pilot study. *BMC Neurology*, *10*, 61. doi.org/10.1186/1471-2377-10-61

Matthews, K. A., Schott, L. L., Brombergere, J. T., Cyranowski, J. M., & Sowers, M. (2010). Are there Bi-directional Associations between Depressive Symptoms and C-Reactive Protein in Mid-life Women? *Brain, Behavior, and Immunity*, *24*(1), 96–101.

doi.org/10.1016/j.immuni.2010.12.017.Two-stage

McAfoose, J., & Baune, B. T. (2009). Evidence for a cytokine model of cognitive function. *Neuroscience and Biobehavioral Reviews*, *33*(3), 355–366. doi.org/10.1016/j.neubiorev.2008.10.005

McCarthy-Jones, S., & McCarthy-Jones, R. (2014). Body mass index and anxiety/depression as mediators of the effects of child sexual and physical abuse on physical health disorders in women. *Child Abuse & Neglect*, *38*(12), 2007–20. doi.org/10.1016/j.chiabu.2014.10.012

McCullough, J. P. (2003). Treatment for chronic depression using Cognitive Behavioral Analysis System of Psychotherapy (CBASP). *Journal of Clinical Psychology*, *59*(8), 833–846. doi.org/10.1002/jclp.10176

Meeusen, R. (2014). Exercise, nutrition and the brain. *Sports Medicine, N.Z.*, *44*, 47–56. doi.org/10.1007/s40279-014-0150-5

Milanschi, Y., Bandinelli, S., Penninx, B., Vogelzangs, N., Corsi, A. M., & Ferucci, L. (2011). Depressive symptoms and inflammation increase in a prospective study of older adults: a protective effect of a healthy (Mediterranean-style) diet. *Molecular Psychiatry*, *16*(6), 589–590. doi.org/10.1002/aur.1474.

Miller, A., & Raison, C. (2015). Are anti-inflammatory therapies viable treatments for psychiatric disorders?: Where the rubber meets the road. *JAMA Psychiatry*, *72*(6), 527–528. doi.org/10.1001/jamapsychiatry.2015.22.

Monje, M. L., Toda, H., & Palmer, T. D. (2003). Inflammatory Blockade Restores Adult Hippocampal Neurogenesis. *Science*, *302*(December), 1760–1765.

Monteiro, S., Ferreira, F. M., Pinto, V., Roque, S., Morais, M., de Sá-Calçada, D., … Cerqueira, J. J. (2016). Absence of IFNγ promotes hippocampal plasticity and enhances cognitive performance. *Translational Psychiatry*, *6*(October 2015), e707. doi.org/10.1038/tp.2015.194

Mueller, T. I., Leon, A. C., Keller, M. B., Solomon, D. A., Endicott, J., Coryell, W., … Maser, J. D. (1999). Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *American Journal of Psychiatry*, *156*(7), 1000–1006. doi.org/10.1176/ajp.156.7.1000

Myint, A.-M., Kim, Y. K., Verkerk, R., Scharpé, S., Steinbusch, H., & Leonard, B. (2007). Kynurenine pathway in major depression: evidence of impaired neuroprotection. *Journal of Affective Disorders*, *98*(1-2), 143–51. doi.org/10.1016/j.jad.2006.07.013

Naismith, S. L., Hickie, I. B., Turner, K., Little, C. L., Winter, V., Ward, P. B., … Parker,

G. (2003). Neuropsychological performance in patients with depression is associated with clinical, etiological and genetic risk factors. *Journal of Clinical and Experimental Neuropsychology*, *25*(August 2014), 866–877. doi.org/10.1076/jcen.25.6.866.16472

Nanni, V., Uher, R., & Danese, A. (2012). Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis. *American Journal of Psychiatry*, *169*(2), 141–151.

Nemeroff, C. B., Heim, C. M., Thase, M. E., Klein, D. N., Rush, J. A., Schatzberg, A. F., Keller, M. B. (2003). Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(24), 14293–14296. doi.org/10.1073/pnas.2336126100

Neu, P., Bajbouj, M., Schilling, A., Godemann, F., Berman, R. M., & Schlattmann, P. (2005). Cognitive function over the treatment course of depression in middle-aged patients: Correlation with brain MRI signal hyperintensities. *Journal of Psychiatric Research*, *39*(2), 129–135. doi.org/10.1016/j.jpsychires.2004.06.004

O´Connor, J. C., Lawson, M. A., Andre, C., Moreau, M., Lestage, J., N., C., … Dantzer, R. (2009). Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Molecular Psychiatry*, *14*(5), 511–522. doi.org/10.1038/sj.mp.4002148.Lipopolysaccharide-induced

Oertel-Knöchel, V., Mehler, P., Thiel, C., Steinbrecher, K., Malchow, B., Tesky, V., Hänsel, F. (2014). Effects of aerobic exercise on cognitive performance and individual psychopathology in depressive and schizophrenia patients. *European Archives of Psychiatry and Clinical Neuroscience*, *264*(7), 589–604. doi.org/10.1007/s00406-014-0485-9

Paivio, S. C. (2001). Stability of retrospective self-reports of child abuse and neglect before and after therapy for child abuse issues. *Child Abuse & Neglect*, *25*, 1053–1068.

Parker, G. (2005). Beyond major depression. *Psychological Medicine*, *35*(4), 467–74. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15856717

Portella, M. J., Marcos, T., Rami, L., Navarro, V., Gastó, C., & Salamero, M. (2003). Residual cognitive impairment in late-life depression after a 12-month period follow-up. *International Journal of Geriatric Psychiatry*, *18*(7), 571–576. doi.org/10.1002/gps.895

Porter, R. J. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *The British Journal of Psychiatry*, *182*, 214–220. doi.org/10.1192/bjp.182.3.214

Porter, R. J., Bourke, C., Carter, J. D., Douglas, K. M., McIntosh, V. V. W., Jordan, J., Frampton, C. M. A. (2016). No change in neuropsychological dysfunction or emotional processing during treatment of major depression with cognitive-behaviour therapy or schema therapy. *Psychological Medicine*, *46*(2), 393–404. doi.org/10.1017/S0033291715001907

Porter, R. J., Bourke, C., & Gallagher, P. (2007). Neuropsychological impairment in major depression: its nature, origin and clinical significance. *The Australian and New Zealand Journal of Psychiatry*, *41*(2), 115–28. doi.org/10.1080/00048670601109881

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*(1), 24–31. doi.org/10.1016/j.it.2005.11.006

Raison, C. L., & Miller, A. H. (2011). Is Depression an Inflammatory Disorder? *Current Psychiatry Reports*, *13*(6), 467–475. doi.org/10.1007/s11920-011-0232-0.Is

Raison, C. L., Rutherford, R. E., Woolwine, B. J., Shuo, C., Schettler, P., Drake, D. F., Miller, A. H. (2013). A randomized controlled trial of the Tumor Necrosis Factor-alpha antagonist infliximab in treatment resistant depression: role of baseline inflammatory biomarkers. *JAMA Psychiatry*, *70*(1), 31–41. doi.org/10.1001/2013.jamapsychiatry.

Rethorst, C. D., Bernstein, I., & Trivedi, M. H. (2014). Inflammation, obesity, and metabolic syndrome in depression: analysis of the 2009-2010 National Health and Nutrition Examination Survey (NHANES). *The Journal of Clinical Psychiatry*, *75*(12), e1428–32. doi.org/10.4088/JCP.14m09009

Richards, D. (2011). Prevalence and clinical course of depression: A review. *Clinical Psychology Review*, *31*(7), 1117–1125. doi.org/10.1016/j.cpr.2011.07.004

Rief, W., Bleichhardt, G., Dannehl, K., Euteneuer, F., & Wambach, K. (2017). Comparing the efficacy of CBASP with two versions of CBT for depression in a routine care center: A randomized clinical trial. *In Preparation*.

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine*, *44*(10), 2029–40. doi.org/10.1017/S0033291713002535

Romano, E., Babchishin, L., Marquis, R., & Frechette, S. (2015). Childhood Maltreatment

and Educational Outcomes. *Trauma, Violence & Abuse*, *16*(4), 418–437. doi.org/10.1177/1524838014537908

Schiffer, A. a, Pelle, A. J., Smith, O. R. F., Widdershoven, J. W., Hendriks, E. H., & Pedersen, S. S. (2009). Somatic versus cognitive symptoms of depression as predictors of all-cause mortality and health status in chronic heart failure. *The Journal of Clinical Psychiatry*, *70*(12), 1667–73. doi.org/10.4088/JCP.08m04609

Seiferth, N. Y., Thienel, R., & Kircher, T. (2007). Exekutive Funktionen. In F. Schneider & G. R. Fink (Eds.), *Funktionelle MRT in Psychiatrie und Neurologie* (pp. 265–277). Berlin, Heidelberg: Springer Berlin Heidelberg. doi.org/10.1007/978-3-540-68558-6_18

Sengupta, P. (2012). Health Impacts of Yoga and Pranayama : A State - of - the - Art Review. *International Journal of Preventive Medicine*, *3*(7), 1–11.

Shapero, B. G., Black, S. K., Liu, R. T., Klugman, J., Bender, R. E., Abramson, L. Y., & Alloy, L. B. (2014). Stressful life events and depression symptoms: the effect of childhood emotional abuse on stress reactivity. *Journal of Clinical Psychology*, *70*(3), 209–23. doi.org/10.1002/jclp.22011

Slopen, N., Kubzansky, L. D., McLaughlin, K. A., & Koenen, K. C. (2013). Childhood adversity and inflammatory processes in youth: A prospective study. *Psychoneuroendocrinology*, *38*(2), 188–200. doi.org/10.1016/j.psyneuen.2012.05.013

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Strauman, T. A., Welsh-bohmer, K., Jeffrey, N., & Sherwood, A. (2011). Aerobic Exercise and Neurocognitive Performance: a Meta-Analytic Review of Randomized Cortrolled Trials. *Psychosomatic Medicine*, *72*(3), 239–252. doi.org/10.1097/PSY.0b013e3181d14633.Aerobic

Smolderen, K., & Spertus, J. (2009). The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circulation: Cardiovascular Quality and Outcomes*, *2*(4), 328–337. doi.org/doi:10.1161/CIRCOUTCOMES.109.868588

Snyder, H. R. (2013). Major Depressive Disorder is Associated with Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review. *Psychological Bulletin*, *139*(1), 81–132. doi.org/10.1037/a0028727

Spann, M. N., Mayes, L. C., Kalmar, J. H., Guiney, J., Womer, F. Y., Pittman, B., … Blumberg, H. P. (2012). Childhood Abuse and Neglect and Cognitive Flexibility in Adolescents. *Child Neuropsychology*, *18*(2), 182–189.

doi.org/10.1080/09297049.2011.595400.

Stewart, J. C., Rand, K. L., Muldoon, M. F., & Kamarck, T. W. (2009). A prospective evaluation of the directionality of the depression-inflammation relationship. *Brain, Behavior, and Immunity*, *23*(7), 936–44. doi.org/10.1016/j.bbi.2009.04.011

Sullivan, P. M. S., & Knutson, J. F. (2000). Maltreatment and Disabilities: A Population-Based Epidemioligical Study. *Child Abuse & Neglect*, *24*(10), 1257–1273.

Sweeney, J. a, Kmiec, J. a, & Kupfer, D. J. (2000). Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biological Psychiatry*, *48*(7), 674–684. doi.org/10.1016/S0006-3223(00)00910-0

Taylor Tavares, J. V., Clark, L., Cannon, D. M., Erickson, K., Drevets, W. C., & Sahakian, B. J. (2007). Distinct Profiles of Neurocognitive Function in Unmedicated Unipolar Depression and Bipolar II Depression. *Biological Psychiatry*, *62*(8), 917–924. doi.org/10.1016/j.biopsych.2007.05.034

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes Martin. *American Journal of Psychiatry*, *170*(10), 1114–1133. doi.org/10.1176/appi.ajp.2013.12070957

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews. Neuroscience*, *17*(10), 652–66. doi.org/10.1038/nrn.2016.111

Thase, M. E. (2013). The multifactorial presentation of depression in acute care. *The Journal of Clinical Psychiatry*, *74 Suppl 2*(suppl 2), 3–8. doi.org/10.4088/JCP.12084su1c.01

Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., … Krishnan, R. (2006). Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. *Lancet*, *367*(9504), 29–35. doi.org/10.1016/S0140-6736(05)67763-X

Tyrka, A. R., Burgers, D. E., Philip, N. S., Price, L. H., & Carpenter, L. L. (2013). The neurobiological correlates of childhood adversity and implications for treatment. *Acta Psychiatrica Scandinavica*, *128*(6), 434–47. doi.org/10.1111/acps.12143

Udina, M., Castellví, P., Moreno-España, J., Navinés, R., Valdés, M., Forns, X., … Martín-Santos, R. (2012). Interferon-Induced Depression in Chronic Hepatitis C. *The Journal of Clinical Psychiatry*, *73*(08), 1128–1138. doi.org/10.4088/JCP.12r07694

Van Veen, T., Wardenaar, K. J., Carlier, I. V. E., Spinhoven, P., Penninx, B. W. J. H., &

Zitman, F. G. (2013). Are childhood and adult life adversities differentially associated with specific symptom dimensions of depression and anxiety? Testing the tripartite model. *Journal of Affective Disorders*, *146*(2), 238–245. doi.org/10.1016/j.jad.2012.09.011

Vares, E. A., Salum, G. A., Spanemberg, L., Caldieraro, M. A., De Souza, L. H., Borges, R. de P., & Fleck, M. P. (2016). Childhood trauma and dimensions of depression: A specific association with the cognitive domain. *Revista Brasileira de Psiquiatria*, *38*(2), 127–134. doi.org/10.1590/1516-4446-2015-1764

Vogelzangs, N., Duivis, H. E., Beekman, A. T., Kluft, C., Neuteboom, J., Hoogendijk, W., … Penninx, B. W. (2012). Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. *Translational Psychiatry*, *2*(2), 1–9. doi.org/10.1038/tp.2012.8

Vythilingam, M., Heim, C., Ph, D., Newport, J., Miller, A. H., Anderson, E., … Nemeroff, C. B. (2002). Childhood trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry*, *159*(12), 2072–2080.

Wang, C. E., Halvorsen, M., Sundet, K., Steffensen, A. L., Holte, A., & Waterloo, K. (2006). Verbal memory performance of mildly to moderately depressed outpatient younger adults. *Journal of Affective Disorders*, *92*(2-3), 283–286. doi.org/10.1016/j.jad.2006.02.008

Wanner, M., Probst-Hensch, N., Kriemler, S., Meier, F., Autenrieth, C., & Martin, B. W. (2016). Validation of the long international physical activity questionnaire: Influence of age and language region. *Preventive Medicine Reports*, *3*, 250–256. doi.org/10.1016/j.pmedr.2016.03.003

Wells, A., Fisher, P., Myers, S., Wheatley, J., Patel, T., & Brewin, C. R. (2009). Metacognitive therapy in recurrent and persistent depression: A multiple-baseline study of a new treatment. *Cognitive Therapy and Research*, *33*(3), 291–300. doi.org/10.1007/s10608-007-9178-2

World Federation For Mental Health (WFMH). (2012). Depression: A Global Crisis. *World Mental Health Day*, 32. Retrieved from http://www.who.int/mental_health/management/depression/wfmh_paper_depression_wmhd_2012.pdf.

Zaninotto, L., Solmi, M., Veronese, N., Guglielmo, R., Ioime, L., Camardese, G., & Serretti, A. (2016). A meta-analysis of cognitive performance in melancholic versus non-melancholic unipolar depression. *Journal of Affective Disorders*, *201*, 15–24.

doi.org/10.1016/j.jad.2016.04.039

9. Appendix

9.1. Studie 1

Childhood adversity and cognitive functioning in patients with major depression

Katharina Dannehl, Winfried Rief, Frank Euteneuer

Division of Clinical Psychology and Psychotherapy, Philipps University Marburg, Germany

Role of funding source:

This study was funded by a grant from the German Research Foundation (DFG) to Dr. Rief (Ri 574/23-1). The DFG had no further role in the study's design or in collecting, analyzing or interpreting study data nor in writing the report or in the decision to submit the paper for publication.

Abstract

Objective: Major depression is often accompanied by deficits in cognitive functioning and lowered executive functions. However, not all depressed patients show impairments in these domains. The aim of this study was to examine whether different kinds of childhood adversity might account for cognitive deficits in patients with major depression.

Methods: Ninety-one patients with major depression (DSM-IV) and 40 healthy controls completed a neuropsychological test battery assessing memory, processing speed and executive functions. The Childhood Trauma Questionnaire (CTQ) was used to measure the severity and number of incidences of sexual, physical and emotional abuse and physical and emotional neglect.

Results: Patients with major depression had a significantly higher number of traumas and reported more severe emotional abuse, emotional neglect and physical neglect than healthy controls. Patients performed less well in memory tasks, general knowledge and processing speed than healthy controls. Hierarchical regression analyses indicated that the overall number of traumas was significantly associated with poorer general knowledge, lower processing speed and impaired executive functions in patients with major depression. A second model including all CTQ-subscales simultaneously demonstrated an association between physical neglect and poorer verbal learning, and physical abuse and diminished executive functions.

Conclusion: A higher number of childhood adversities may influence general knowledge, processing speed and executive functions in patients with major depression. In addition, physical abuse and neglect seemed to be associated with verbal learning deficits and poorer executive functions.

Keywords: major depression disorder, cognitive function, executive function, childhood adversity

Introduction

A growing body of evidence suggests an association between childhood adversity and the development and course of major depressive (MD) (Kessler, 1997; Kessler et al., 2010). Meta-analytic results have revealed an association between sexual and physical abuse experienced in childhood and higher levels of depression in adulthood (Lindert et al., 2013). The severity of emotional abuse might be associated with depressive symptoms in adults (Shapero et al., 2014). Childhood adversities seem to influence an earlier onset of depression, the number of depressive episodes and its more chronic course (Gillespie & Nemeroff, 2005; Klein et al., 2009).

An explanation for this association is offered by hypothalamic-pituitary-adrenal axis (HPA axis) hyperreactivity. Heim et al (2008) demonstrated that HPA axis hyperreactivity might be a consequence of childhood abuse and several studies report the influence of the HPA axis itself on depression (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; for an overview see Stetler & Miller, 2011) Another proposed pathway involves the brain-derived neurotrophic factor (BNDF). Plasma BNDF has appeared lower in depressed women with a history of physical neglect compared to nonabused depressed women and controls (Grassi-Oliveira, Stein, Lopes, Teixeira, & Bauer, 2008). In addition, maltreatment in childhood seems to be associated with enduring immune and metabolic abnormalities which in turn might be important factors in the pathophysiology of depression (Slopen, Kubzansky, McLaughlin, & Koenen, 2013; Danese et al., 2013).

Childhood adversity has also been linked to poor cognitive functioning in adulthood. An association between emotional abuse and physical neglect in childhood and worse memory performance has been identified in healthy populations, but no association was observed between any type of childhood adversity and executive functions, psychomotor speed or attention (Majer, Nater, Lin, Capuron, & Reeves, 2010). Spann et al (2012) demonstrated an association between physical abuse/neglect and diminished cognitive flexibility in adolescence. Contrary findings have also been reported: a population-based study of adults aged 50 years and older revealed an association between sexual abuse in childhood and better global cognition, memory, executive function and processing speed (Feeney, Kamiya, Robertson, & Kenny, 2013). In a sample of individuals over 65 years, Ritchie et al (2011) showed that experiencing physical, mental or sexual abuse was associated with a lower risk of cognitively impaired verbal fluency.

Impaired memory and executive functions are common features in MD. Although many meta-analyses have confirmed the association between depression and different

kinds of cognitive impairment (Burt, Zembar, & Niederehe, 1995; Hammar & Ardal, 2009; Veiel, 1997 Lee, Hermens, Porter, & Redoblado-Hodge, 2012), not all patients with MD show cognitive deficits (Porter, Bourke, & Gallagher, 2007). So far, only one study examined childhood maltreatment as a potential explanation for poor cognitive functioning in MD (Gould et al., 2012). The authors detected an association between early life adversities and cognitive deficits, but only in a mixed sample containing healthy participants, patients with MD and those with PTSD.

To overcome these limitations, we aimed to investigate a sample of patients specifically diagnosed with MD and a healthy control sample. Neuropsychological functions were to be investigated in detail, paying particular attention to the role of different kinds of childhood adversities for explaining cognitive deficits in depression. Such knowledge might help prevent major depression and identify the appropriate treatment of this heterogeneous disorder.

Method

Participants

Patients were recruited via the Outpatient Clinic for Psychological Interventions of the University of Marburg via advertisements, leaflets in pharmacies and waiting rooms of doctors and press releases in local papers. A high number of patients participated in a larger longitudinal study after completing assessments for the present purpose. A sample of 40 non-depressed age- and sex-matched healthy controls from the same community was involved to examine potential baseline alterations in cognitive functioning in MD. Healthy controls were recruited via advertisements and press releases in local papers. The study was approved by the ethics committees of the German Psychological Society.

Procedure

All participants underwent a diagnostic session which included the structured clinical interview for DSM-IV (SCID) and an interview that focused on exclusion criteria and demographic variables. Exclusion criteria were neurological illness, psychotic symptoms, alcohol and/or drug abuse, antipsychotics, stimulants, current pregnancy and lactation in women and any psychiatric diagnosis according to DSM-IV in controls. After the diagnostic session and having provided informed consent, individuals were invited for neuropsychological tests on the following days. All participants were tested between 7:00 am and 10:00 am in the same test order as follows:

1) Mini Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975): general cognitive status
2) Logical Memory Test 1 (LM, Härting et al., 2000): verbal learning and memory
3) Trail Making Test A and B (TMT, Reitan & Wolfson, 1985): processing speed and executive functions (cognitive flexibility, working memory, set-shifting abilities)
4) Modified Card Sorting Test (computer version, Nelson, 1976): executive functions (categorization, set-shifting, cognitive flexibility, perseveration, the ability to utilize feedback)
5) Digit span subtest of the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 2008): memory, working memory, attention
6) *Subtest "general knowledge"* of the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 2008): semantic memory
7) Logical Memory Test 2 (LM 2): verbal learning and memory
8) Verbal learning and memory test (VLMT, Helmstaedter, Lendt, & Lux, 2001): verbal learning and memory

Measures

Psychopathology and childhood adversity

As mentioned above, we applied the SCID to confirm the diagnosis of major depression and to specify the depressive subtype and comorbid axis-I disorders. Furthermore, we noted the time of onset of the first depressive episode, the number of depressive episodes and a potentially chronic course of depression. Each participant's symptom severity was assessed via the Beck Depression Inventory (BDI, Beck & Steer, 1987, Hautzinger, Bailer, Worall, & Keller, 1995). To assess childhood abuse and neglect experiences, the Childhood Trauma Questionnaire (CTQ) was used. The CTQ is a 28item, self-report questionnaire used to assess sexual, physical and emotional abuse, and physical and emotional neglect. Each item is rated on a five-point Likert-type scale from "never true" to "very often true" (Bernstein et al., 1994). The CTQ has been proven to be a reliable and valid screening for the retrospective assessment of child maltreatment (Klinitzke, Romppel, Häuser, Brähler, & Glaesmer, 2012).

Neuropsychological battery

Global cognitive function

General cognitive status was assessed by the Mini Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975, Kessler, Markowitsch, & Denzler, 1990) (inclusion criterion: ≥25 points) to control for dementia in patients and controls.

Memory

To measure verbal learning and memory, the subtests "logical memory 1 and 2" of the Wechsler Memory Scale-R (WMS-R, Härting 2000) and a German adaptation of the "Rey auditory Verbal Learning Test" were administered (VLMT, *Helmstaedter C. Lendt M. & Lux S. 2001)*. In the Logical Memory (LM) task, the verbal recall of two orally-presented story passages is required immediately after their presentation and after a retention interval (about 30 min). The VLMT requires the learning and immediate recall of a list of 15 items during five learning trials, one-time presentation and immediate free recall of a distractor list of the same length, free recall of the items after distraction, free recall after a filled retention interval (about 20 min) and delayed yes–no recognition. The total number of items reproduced during the five learning trials (verbal learning performance score), the reproduced distractor words (recall of distractor words), the loss in delayed free recall as compared with the last learning trial (verbal retention performance score) and the number of correctly recognized words during yes-no recognition (verbal recognition performance score) were measured.

Semantic memory was assessed via t*he subtest "general knowledge"* of the WAIS (Wechsler, 2008) measuring participants' ability to gain, maintain and reproduce general knowledge.

Processing Speed and Executive functions

Executive functions were investigated using a computerized version of the Modified Card Sorting Test (MCST) (Nelson, 1976), the Trail Making Test A and B (Reitan & Wolfson, 1985) and the digit span subtest of the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 2008). In the MCST, subjects are asked to place a total of 48 cards one by one below four different stimulus cards. Subjects have to learn possible sorting rules by using the feedback (correct or wrong) from previous trials. After six correct responses, the sorting rule changes and subjects must adapt to the new rule. The MCST assesses categorization, set-shifting, cognitive flexibility, perseveration and the ability to utilize feedback

(Strauss, Sherman, & Spreen, 2006). The Trail Making Test (TMT) is built up of the TMT-A in which participants have to connect numbers (1–25) in an ascending order and the TMT-B which requires connecting numbers (1–13) and letters (A–L) alternately. Both measure processing speed and visual scanning abilities, moreover, the TMT-B assesses cognitive flexibility, working memory and set-shifting abilities. In the digit span subtest of the WAIS, participants receive a set of numbers and are asked to repeat them in the correct order and then in the opposite order in which they were given.

Statistical analysis

The statistical analyses were carried out with SPSS version 22.0 for Windows (Chicago, SPSS, Inc.). Boxplots were used to control for univariate outliers. Group differences were calculated using analyses of variance and χ^2 tests. Separate hierarchical linear regression models were conducted for patients with MD and healthy controls to examine whether the overall number of childhood traumas or specific forms of adversities predicts depression severity and cognitive impairment after adjusting for age, gender and education. The residuals of all linear regression models were normally distributed (Durban–Watson-Test) and variance inflation factors were below 1.8 for all variables in all models, indicating that multicollinearity did not appear to be a concern (Stevens, 2002; Tabachnick & Fidell, 2001)

As suggested by Lazzeroni et al and Rothman, we did not correct for multiple testing due to the exploratory nature of our study (Lazzeroni & Ray, 2012; Rothman, 1990). Post-hoc power calculations were done and account for a sample-size of 91 patients a statistical power of $1-\beta= 0.80$ and a level of significance of $\alpha<.05$ with an expected medium effect ($f^2=0.15$), (Cohen, 1988; Faul, Erdfelder, Lang, & Buchner, 2007)

Results

Demographics and Clinical Characteristics

Characteristics of participants and group differences are presented in Table 1. Patients with major depression and controls were comparable with respect to age, education, sex and body mass index (BMI) ($p>0.1$), but differed significantly in all psychopathological measures ($p<0.001$) except the sexual abuse and physical abuse CTQ-subscales.

Cognitive performance

Patients with MD demonstrated worse cognitive performance than healthy controls in memory, as revealed by the verbal learning performance score on the VLMT (F (1, 129) =5.01, p<0.05) and the ability to recall the distractor words on the VLMT (F (1, 128) =4.7, p<0.05). Furthermore, patients scored lower in processing speed, tested by the TMT-A (F (1, 129) =9.22, p<0.005) and in semantic memory as assessed by the subtest *"general knowledge"* of the WAIS (F (1, 129) =5.00, p < 0.05) than healthy controls. We observed no differences in memory assessed in terms of the verbal retention performance score, the VLMT's verbal recognition performance score and the logical memory tasks, as well as in any test of executive functions (p>0.05) (table 1).

Here Table 1

Childhood adversities and cognitive performance in Patients with MD

Patients with MD reporting childhood adversities presented significantly lower results in general knowledge (F (1, 84) = 6.27, p<0.01) and TMT-A (F (1, 84) = 4.71, p<0.05) than patients with major depression without childhood adversities. No significant differences were found among all the other cognitive tests (p>0.5). Furthermore, patients with MD reporting any kind of childhood adversity and those reporting none, did not differ in depression severity.

To examine whether the number of reported adversities or specific kinds of childhood adversities predict particular cognitive impairments, we assessed the relationship between the CTQ-subscales (independent variables) and cognitive functioning (dependent variables). Table 2 and 2b illustrates results from the hierarchical linear regression analysis. After adjusting for the covariates age, gender and education (step 1), the number of adversities respectively the CTQ-subscales were entered on step 2.

The results indicated that the number of traumas significantly predicted poorer performance on TMT-A (β = .22, ΔR^2 = 0.03, p<.05), on general knowledge (β = -.25, ΔR^2 = 0.06, p<.01) and on MCST in patients with MD, as measured by the number of false responses (β = .20, ΔR^2 = 0.04, p<.05).

In a further model, all CTQ-subscales were entered simultaneously on step 2. The subscale physical neglect predicted a significantly poorer performance recalling distractor words on the VLMT (β = -.30, p<.05), while physical abuse predicted worse performance

on the TMT-B (β = .22, p<.05). Moreover, physical abuse was associated with a higher rate of false responses during the MCST (β = .22, p<.05). In contrast, the "emotional abuse" subscale was associated with a better performance in executive functions, measured by a higher number of correct responses in the MCST (β = .40, $\Delta R^2 = 0.11$, $p < .05$) and a lower number of perseverations (β = -0.3, p<.05). We observed no significant relationships among childhood adversities and the digit span subtests on the WAIS, Logical Memory tasks or the VLMT's verbal recognition performance score in patients with MD.

Here table 2 and 2b

Childhood adversities and cognitive performance in healthy controls

Exploratory analyses for healthy controls indicated that the "emotional neglect" subscale predicted significantly poorer performance in the WAIS' digit span subtest (β = -.45, p<.05). No significant relationships were apparent among childhood adversities and memory, processing speed or executive functions measured by the MCST.

Discussion

The present study confirmed impaired memory, semantic memory and processing speed in patients with MD compared to healthy controls. Our results reveal no differences between patients with MD and healthy controls in executive functions. Detailed analyses of patients with MD revealed that patients reporting a higher total number of childhood traumas performed worse in processing speed, semantic memory and executive functions. The subscales physical neglect and physical abuse appeared to be associated with worse verbal learning abilities, diminished working memory and lowered executive functions. Contrary to our expectations, the CTQ-subscale "emotional abuse" seemed to correlate with better performance in executive function tests in patients with MD.

Our finding that patients reporting a higher number of childhood adversities also demonstrate diminished semantic memory skills, lower processing speed and more false responses in the MCST confirms and expands upon previous research (De Bellis, Woolley, & Hooper, 2013; van der Heijden, Suurland, Swaab, & de Sonneville, 2011). We therefore assume that adversities have a cumulative effect. In addition to that we demonstrated that different kinds of childhood adversities might have a different influence on future cognitive deficits in depression. These results are in line with Schilling et al, who suggested that

the severity of experienced childhood adversities might influence mental health and that different kinds of maltreatments may differently affect mental health outcomes (Schilling, Aseltine, & Gore, 2008).

Although we did not examine longitudinal biological pathways between childhood adversities and cognitive functioning, there are a number of potential mechanisms, which might be of interest considering our findings. For example, childhood adversities might be perceived as persistent stress attended by glucocorticoid activation and subsequent suppressed information processes, which might explain diminished semantic memory skills (Sauro, Jorgensen, & Pedlow, 2003; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; van der Heijden et al., 2011). Moreover, childhood adversities appear to be associated with a special sensitization to stress responses (Heim et al., 2000). Cognitive tests, potentially perceived as stressors might be accompanied by glucocorticoid secretion and a following worse performance (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). Finally, impaired semantic memory skills might be associated with reduced hippocampal volume caused by enduring stress in childhood (Carrion, Weems, & Reiss, 2007; van der Heijden et al., 2011; Vythilingam et al., 2002).

Our detected association between physical abuse/physical neglect and diminished power in speed, cognitive flexibility, working memory and set-shifting abilities and more false responses in the MCST, confirms prior research in non-depressed samples. Aas et al (2012) demonstrated a relationship between physical abuse and diminished working memory and executive functions in patients with schizophrenia. Significant correlations were identified in samples of healthy adolescents in terms of physical abuse/neglect with more perseveration errors, while emotional abuse/neglect revealed no effects on cognitive functioning (Aas et al., 2012; Spann et al., 2012). These findings suggest that physical abuse/neglect (e.g. deficient nutrition, a lack of medical care or beatings) have a more critical influence on neurodevelopment than emotional deprivation. Dietary factors, especially malnutrition and being overweight, seem to exert broad influence on neuronal function and plasticity (McCarthy-Jones & McCarthy-Jones, 2014; Meeusen, 2014). An excessive Body Mass Index is often associated with reduced physical activity and higher inflammatory markers, and both might have a negative influence on cognitive functioning (Erickson, Miller, & Roecklein, 2012; Green & Nolan, 2014; Smith et al., 2011).

Some maintain that there are some children's characteristics that seem to make them prone to physical abuse and neglect and which need consideration when interpreting neuropsychological results. Mental health or developmental problems, verbal and physical

aggression or impulsive behavior might increase the risk for experiencing adversities (Hadianfard, 2014; Sullivan & Knutson, 2000). Simultaneously, we can assume that these characteristics also predict diminished cognitive functioning in adulthood.

In our study, emotional abuse was associated with better executive functions. Enduring emotional abuse might contribute to greater vigilance and monitoring of the environment and thus to handling of executive functioning tasks more cautiously. Furthermore it is possible that children experiencing emotional abuse still grow up within an enriched environment, which in turn seems to have positive effects on neurotransmitter activation and neurodevelopment (Praag, Kempermann, & Gage, 2000). Overall, nature and the intensity and dose of adversities seem to have different effects on cognitive functioning.

Contrary to prior research we identified no difference in executive functions between patients and healthy controls. Samples of elderly patients have demonstrated executive dysfunction in MD as have inpatients, patients with depression and comorbid anxiety, and patients suffering from particularly severe episodes of depression (Basso et al., 2007; Fossati et al., 2004; Harvey et al., 2004; Lockwood, Alexopoulus, & van Gorp, 2002; Lyche, Jonassen, Stiles, Ulleberg, & Landrø, 2011; Snyder, 2014b). In contrast, our sample consisted of middle-aged (age MD=37.4) outpatients and only 13 patients (12%) reported comorbid anxiety. This might explain our divergent findings.

Our study has some limitations. Although previous researchers found the CTQ to be an acceptable stable instrument even in the context of reduced psychopathology (Hardt & Rutter, 2004; Lizardi & Klein, 2005; Paivio, 2001), we assessed childhood adversities retrospectively, a factor prone to memory bias. Though especially adversities in childhood seem to have an impact on future psychopathology, we did not control for maltreatment in adulthood, which might have an influence as well. All patients were recruited via the Outpatient Clinic for Psychological Interventions. Thus, our sample consists of outpatients with MD who were eligible for psychological treatment, and findings may not generalize to other samples of patients (e.g., MD patients with psychotic features). Furthermore, due to the cross-sectional assessment of cognitive function, causal interpretations cannot be made. Longitudinal studies are needed to confirm and extend our results.

In conclusion: our results suggest a cumulative effect from the number of childhood adversities on cognitive functioning in patients with major MD. Physical abuse and neglect seem to have a more critical influence on verbal learning abilities, working memory, and executive functions than emotional abuse and neglect. These findings might help to explain the heterogeneity of cognitive function in patients with depression. Fur-

thermore, our results provide evidence for the importance of neuropsychological interventions when treating of depressive patients and when designing early interventions that could mitigate the impact of childhood adversity on cognitive functioning.

Conflict of interest

None.

Acknowledgments

We wish to thank all participants.

Table 1
Sociodemographic characteristics, psychopathological measures and neuropsychological test scores for patients with major depression (MD) and healthy controls (HC).

	MD (n = 91)	HC (n = 40)	*p*
Sociodemographic data			
Age	37.41 (12.4)	34.32 (11.62)	0.175
Gender: female. N (%)	58 (61,1)	26 (66.7)	0.542
Years of education	10.17 (11.45)	12.34 (1.37)	0.229
Body mass index. kg/m^2	25.50 (5.18)	23.75 (4.26)	0.081
Use of antidepressiva: yes (%)	41 (43.6)	-	-
DSM-IV comorbidity. n (%)			
Undifferentiated somatization disorder	3 (3.3)	-	
Panic disorder	7 (7.5)	-	
Generalized anxiety disorder	1 (1.1)	-	
Social phobia	2 (2.1)	-	
Specific phobia	3 (3.3)	-	
Obsessive Compulsive Disorder	1 (1.1)	-	
Psychopathological measures			
Becks Depression Inventory (BDI-II)	26.40 (8.81)	3,34 (2.92)	**0.001**
Global Severity Index (GSI)	1.09 (0.53)	0.16 (0.13)	**0.001**
Childhood Trauma Questionnaire (CTQ)			
Reporting any Trauma N (%)	68 (74,7)	7 (17,9)	**0.004**
Total Score	44.82 (8.45)	34.64 (9.52)	**0.001**
Emotional abuse	9.60 (4.61)	7.61 (3.58)	**0.019**
Physical abuse	6.35(2.98)	5.54 (1.30)	0.105
Sexual abuse	5.65 (2.24)	5.46 (1.35)	0.583
Emotional neglect	15.60 (4.47)	9.79 (4.73)	**0.001**
Physical neglect	7.64 (2.80)	6.23 (1.81)	**0.005**
Number of traumas	0.89 (0.67)	0.26 (0.59)	**0.001**
Neuropsychological tests			
Logical memory 1	27.28 (7.77)	26.53 (8.60)	0.630
Logical memory 2	23.32 (8.23)	23.10 (8.90)	0.894
VLMT verbal learning performance score	53.50 (11.09)	57.87 (7.65)	**0.027**
VLMT recall of distractor words	5.94 (2.09)	6.82 (2.14)	**0.032**
VLMT verbal retention performance score	1.61 (2.25)	1.10 (2.19)	0.242
VLMT verbal recognition performance score	14.20 (1.31)	14.60 (0.71)	0.076
Semantic memory	18.27 (6.00)	20.67 (4.50)	**0.027**
MCST correct	33.90 (7.11)	33.21 (7.90)	0.638
MCST false*	8.13(6.71)	7.70 (6.63)	0.732
MCST perseveration	2.33 (3.14)	3.10 (5.30)	0.336
TMT-A*	31.78 (10.25)	25.94 (9.52)	**0.003**
TMT-B*	61.91 (23.03)	55.26 (22.03)	0.130
digit span forward	9.61 (1.89)	9.87 (2.73)	0.528
digit span backward	6.79 (2.06)	7.10 (2.83)	0.486

Note. Group differences were calculated by analyses of variance for continuous variables and χ^2 -tests for categorical variables. Values are shown as mean (SD) unless otherwise noted. * higher values illustrate worse performance

Table 2 Regression of the overall number of trauma on cognitive domains

Variable	**Number of Traumas**		
	β	**R²**	**Δ R²**
Logical memory 1	-0.20	0.16	0.04
Logical memory 2	-0.18	0.16	0,03
VLMT verbal learning performance score	-0.19	0.32	0.03
VLMT recall of distractor words	-0.18	0.12	0.03
VLMT verbal retention performance score	-0.08	0.17	0.005
VLMT verbal recognition performance score	-0.04	0.13	0.002
Semantic memory	**-0.25****	0.31	**0.06****
MCST correct	-0.10	0.24	0.01
MCST false [a)]	**0.20***	0.32	**0.04***
MCST perseveration	0.03	0.25	0.001
TMT-A [a)]	**0.22***	0.32	**0.03***
TMT-B [a)]	0.09	0.33	0.01
digit span forward	-0.09	0.07	0.01
digit span backward	-0.01	0.18	0.01

Note. β standardized regression coefficient; R^2 total variance explained by the model; ΔR^2 = variance explained by the number of traumas after adjusting for age, gender and education * $p < .05$. ** $p < .01$. *** $p < .001$. [a)] higher values illustrate worse performance

Table 2b Regression of all CTQ-Subscales on neuropsychological tests.

Variable			Emotional abuse	Physical abuse	Sexual abuse	Emotional neglect	Physical neglect
	R^2	ΔR^2	β				
Logical memory 1	0.18	0.05	0.05	-0.07	-0.08	-0.05	-0.22
Logical memory 2	0.19	0.06	-0.02	-0.11	-0.09	0.05	-0.11
VLMT verbal learning performance score	0.32	0.04	0.04	-0.12	-0.07	0.9	-0.8
VLMT recall of distractor words	0.17	0.82	0.03	-0.01	-0.01	0.05	**-0.30***
VLMT verbal retention performance score	0.22	0.04	-0.01	-0.01	0.18	-0.09	-0.03
VLMT verbal recognition performance score	0.14	0.01	0.08	-0.01	0.01	0.04	-0.09
General knowledge (semantic memory)	0.30	0.05	0.05	-0.11	-0.08	-0.10	-0.20
MCST correct	0.30	**0.11***	0.30	**0.40****	-0.19	-0.07	-0.15
MCST false	0.34	0.06	-0.20	**0.22***	0.08	0.15	0.12
MCST perseveration	0.33	0.08	**-0.30***	0.15	0.02	0.15	0.04
TMT-A	0.25	0.04	-0.16	0.13	0.07	0.01	0.14
TMT-B	0.41	0.05	-0.22	**0.22***	0.05	-0.03	0.13
Digit span forward	0.11	0.05	0.08	0.03	**-0.24***	-0.05	-0.04
Digit span backward	0.22	0.04	0.11	0.01	-0.16	0.02	-0.14

Note. β standardized regression coefficient; R^2 total variance explained by the model; ΔR^2 = variance explained by the CTQ-Subscales after adjusting for age, gender and education
* $p < .05$. ** $p < .01$.

References

Aas, M., Steen, N. E., Agartz, I., Aminoff, S. R., Lorentzen, S., Sundet, K., & Melle, I. (2012). Is cognitive impairment following early life stress in severe mental disorders based on specific or general cognitive functioning? *Psychiatry Research*, *198*(3), 495–500. http://doi.org/10.1016/j.psychres.2011.12.045

Basso, M. R., Lowery, N., Ghormley, C., Combs, D., Purdie, R., Neel, J., & Bornstein, R. (2007). Comorbid anxiety corresponds with neuropsychological dysfunction in unipolar depression. *Cognitive Neuropsychiatry*, *12*(5), 437–56. http://doi.org/10.1080/13546800701446517

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., … Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry*, *151*(8), 1132–6. http://doi.org/10.1176/ajp.151.8.1132

Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin*, *117*(2), 285–305. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7724692

Carrion, V. G., Weems, C. F., & Reiss, A. L. (2007). Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. *Pediatrics*, *119*(3), 509–16. http://doi.org/10.1542/peds.2006-2028

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Hillsdale, NJ: Erlbaum, Lawrence.

Danese, A., Moffitt, T. E., Harrington, H., Milne, B. J., Polanczyk, G., Pariante, C. M., … Caspi, A. (2013). Adverse Childhood Experiences and Adult Risk Factors for Age-Related Disease: Depression, Inflammation, and Clustering of Metabolic Risk Markers. *Archives of Pediatrics and Adolescent Medicine*, *163*(12), 1135–1143.

http://doi.org/10.1001/archpediatrics.2009.214.

De Bellis, M. D., Woolley, D. P., & Hooper, S. R. (2013). Neuropsychological findings in pediatric maltreatment: relationship of PTSD, dissociative symptoms, and abuse/neglect indices to neurocognitive outcomes. *Child Maltreatment*, *18*(3), 171–83. http://doi.org/10.1177/1077559513497420

Erickson, K. I., Miller, D. L., & Roecklein, K. a. (2012). The aging hippocampus: interactions between exercise, depression, and BDNF. *The Neuroscientist*, *18*(1), 82–97. http://doi.org/10.1177/1073858410397054

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. http://doi.org/10.3758/BF03193146

Feeney, J., Kamiya, Y., Robertson, I. H., & Kenny, R. A. (2013). Cognitive Function Is Preserved in Older Adults With a Reported History of Childhood Sexual Abuse. *Journal of Traumatic Stress*, *26*(6), 735–743. http://doi.org/10.1002/jts.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). “Mini -Mental State” A practical state method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research*, *12*, 189–198.

Fossati, P., Harvey, P.-O., Le Bastard, G., Ergis, A.-M., Jouvent, R., & Allilaire, J.-F. (2004). Verbal memory performance of patients with a first depressive episode and patients with unipolar and bipolar recurrent depression. *Journal of Psychiatric Research*, *38*(2), 137–144. http://doi.org/10.1016/j.jpsychires.2003.08.002

Gillespie, C. F., & Nemeroff, C. B. (2005). Early Life Stress and Depression. Childhood trauma may lead to neurobiologically unique mood disorders. *Current Psychiatry*, *4*(10).

Gould, F., Clarke, J., Heim, C., Harvey, P. D., Majer, M., & Nemeroff, C. B. (2012). The

effects of child abuse and neglect on cognitive functioning in adulthood. *Journal of Psychiatric Research*, *46*(4), 500–6. http://doi.org/10.1016/j.jpsychires.2012.01.005

Grassi-Oliveira, R., Stein, L. M., Lopes, R. P., Teixeira, A. L., & Bauer, M. E. (2008). Low plasma brain-derived neurotrophic factor and childhood physical neglect are associated with verbal memory impairment in major depression--a preliminary report. *Biological Psychiatry*, *64*(4), 281–5. http://doi.org/10.1016/j.biopsych.2008.02.023

Green, H. F., & Nolan, Y. M. (2014). Inflammation and the developing brain: consequences for hippocampal neurogenesis and behavior. *Neuroscience and Biobehavioral Reviews*, *40*, 20–34. http://doi.org/10.1016/j.neubiorev.2014.01.004

Hadianfard, H. (2014). Child abuse in group of children with attention deficit-hyperactivity disorder in comparison with normal children. *International Journal of Community Based Nursing and Midwifery*, *2*(2), 77–84. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4201192&tool=pmcentrez&rendertype=abstract

Hammar, A., & Ardal, G. (2009). Cognitive functioning in major depression--a summary. *Frontiers in Human Neuroscience*, *3*(September), 26. http://doi.org/10.3389/neuro.09.026.2009

Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of Child Psychology and Psychiatry*, *45*(2), 260–273. http://doi.org/10.1111/j.1469-7610.2004.00218.x

Härting, C., Markowitsch, H.-J., Neufeld, H., Calabrese, P., Deisinger, K., & Kessler, J. (2000). *Wechsler Memory Scale - Revised Edition* (German Edi). Bern: Huber.

Harvey, P. O., Le Bastard, G., Pochon, J. B., Levy, R., Allilaire, J. F., Dubois, B., & Fossati, P. (2004). Executive functions and updating of the contents of working memory in unipolar depression. *Journal of Psychiatric Research*, *38*(6), 567–76.

http://doi.org/10.1016/j.jpsychires.2004.03.003

Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., … Nemeroff, C. B. (2000). Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood. *The Journal of the American Medical Association*, *284*(5), 3–8. http://doi.org/10.1001/jama.284.5.592

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*, *33*(6), 693–710. http://doi.org/10.1016/j.psyneuen.2008.03.008

Helmstaedter, C., Lendt, M., & Lux, S. (2001). VLMT Verbaler Lern- und Merkfähigkeitstest. *Göttingen: Beltz Test GmbH*.

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology*, *48*, 191–214. http://doi.org/10.1146/annurev.psych.48.1.191

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. a, Zaslavsky, A. M., … Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *The British Journal of Psychiatry : The Journal of Mental Science*, *197*(5), 378–85. http://doi.org/10.1192/bjp.bp.110.080499

Klein, D. N., Ph, D., Arnow, B. A., Barkin, J. L., Dowling, F., Kocsis, J. H., … Wisniewski, S. R. (2009). Early Adversity in Chronic Depression: Cinical Correlates and Response to Pharmacotherapy. *Depression and Anxiety*, *26*, 701–710. http://doi.org/10.1002/da.20577.

Klinitzke, G., Romppel, M., Häuser, W., Brähler, E., & Glaesmer, H. (2012). The German Version of the Childhood Trauma Questionnaire (CTQ): psychometric characteristics in a representative sample of the general population. *Psychotherapie, Psychosomatik, Medizinische Psychologie*, *62*(2), 47–51. http://doi.org/10.1055/s-0031-1295495

Lazzeroni, L. C., & Ray, A. (2012). The cost of large numbers of hypothesis tests on power, effect size and sample size. *Molecular Psychiatry*, *17*(1), 108–14. http://doi.org/10.1038/mp.2010.117

Lindert, J., von Ehrenstein, O. S., Grashow, R., Gal, G., Braehler, E., & Weisskopf, M. G. (2013). Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: systematic review and meta-analysis. *International Journal of Public Health*, 359–372. http://doi.org/10.1007/s00038-013-0519-5

Lizardi, H., & Klein, D. N. (2005). Long-Term Stability of Parental Representations in Depressed Outpatients Utilizing the Parental Bonding Instrument. *The Journal of Nervous and Mental Disease*, *193*(3), 183–188. http://doi.org/10.1097/01.nmd.0000154838.16100.36

Lockwood, K. A., Alexopoulus, G. S., & van Gorp, W. G. (2002). Executive dysfunction in geriatric depression. *The American Journal of Psychiatry*, *159*(7), 1119–1126. http://doi.org/10.1176/appi.ajp.159.7.1119

Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition*, *65*(3), 209–37. http://doi.org/10.1016/j.bandc.2007.02.007

Lyche, P., Jonassen, R., Stiles, T. C., Ulleberg, P., & Landrø, N. I. (2011). Attentional Functions in Major Depressive Disorders With and Without Comorbid Anxiety. *Archives of Clinical Neuropsychology*, *26*, 38–47. http://doi.org/10.1093/arclin/acq095

Majer, M., Nater, U. M., Lin, J.-M. S., Capuron, L., & Reeves, W. C. (2010). Association of childhood trauma with cognitive function in healthy adults: a pilot study. *BMC Neurology*, *10*, 61. http://doi.org/10.1186/1471-2377-10-61

McCarthy-Jones, S., & McCarthy-Jones, R. (2014). Body mass index and anxiety/depression as mediators of the effects of child sexual and physical abuse on physical health disorders in women. *Child Abuse & Neglect*, *38*(12), 2007–20. http://doi.org/10.1016/j.chiabu.2014.10.012

Meeusen, R. (2014). Exercise, nutrition and the brain. *Sports Medicine, N.Z.*, *44*, 47–56. http://doi.org/10.1007/s40279-014-0150-5

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex*, *12*(4), 313–324.

Paivio, S. C. (2001). Stability of retrospective self-reports of child abuse and neglect before and after therapy for child abuse issues. *Child Abuse & Neglect*, *25*, 1053–1068.

Porter, R. J., Bourke, C., & Gallagher, P. (2007). Neuropsychological impairment in major depression: its nature, origin and clinical significance. *The Australian and New Zealand Journal of Psychiatry*, *41*(2), 115–28. http://doi.org/10.1080/00048670601109881

Praag, H. Van, Kempermann, G., & Gage, F. H. (2000). Neural consequences of environmental enrichment. *Neuroscience. Nature Reviews*, *1*(December), 1–8. http://doi.org/10.1038/35044558

Reitan, R. M., & Wolfson, D. (1985). *The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and clinical interpretation.* Tuscon, AZ: Neuropsychological Press.

Rothman, K. J. (1990). No Adjustments Are Needed for Multiple Comparisons. *Epidemiology*, *1*(1), 43–46. http://doi.org/10.1097/00001648-199001000-00010

Sauro, M. D., Jorgensen, R. S., & Pedlow, C. T. (2003). Stress, glucocorticoids, and memory: a meta-analytic review. *Stress (Amsterdam, Netherlands)*, *6*(4), 235–45. http://doi.org/10.1080/10253890310001616482

Schilling, E. A., Aseltine, R. H., & Gore, S. (2008). The impact of cumulative childhood adversity on young adult mental health: Measures, models, and interpretations. *Social Science and Medicine*, *66*(5), 1140–1151. http://doi.org/10.1038/jid.2014.371

Schwabe, L., Joëls, M., Roozendaal, B., Wolf, O. T., & Oitzl, M. S. (2012). Stress effects on memory: an update and integration. *Neuroscience and Biobehavioral Reviews*, *36*(7), 1740–9. http://doi.org/10.1016/j.neubiorev.2011.07.002

Shapero, B. G., Black, S. K., Liu, R. T., Klugman, J., Bender, R. E., Abramson, L. Y., & Alloy, L. B. (2014). Stressful life events and depression symptoms: the effect of childhood emotional abuse on stress reactivity. *Journal of Clinical Psychology*, *70*(3), 209–23. http://doi.org/10.1002/jclp.22011

Slopen, N., Kubzansky, L. D., McLaughlin, K. A., & Koenen, K. C. (2013). Childhood adversity and inflammatory processes in youth: A prospective study. *Psychoneuroendocrinology*, *38*(2), 188–200. http://doi.org/10.1016/j.psyneuen.2012.05.013

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Strauman, T. A., Welsh-bohmer, K., Jeffrey, N., & Sherwood, A. (2011). Aerobic Exercise and Neurocognitive Performance: a Meta-Analytic Review of Randomized Cortrolled Trials. *Psychoso*, *72*(3), 239–252. http://doi.org/10.1097/PSY.0b013e3181d14633.

Snyder, H. R. (2014). Major Depressive Disorder is Associated with Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review. *Psychological Bulletin*, *139*(1), 81–132. http://doi.org/10.1037/a0028727.

Spann, M. N., Mayes, L. C., Kalmar, J. H., Guiney, J., Womer, F. Y., Pittman, B., … Blumberg, H. P. (2012). Childhood Abuse and Neglect and Cognitive Flexibility in Adolescents. *Child Neuropsychology*, *18*(2), 182–189. http://doi.org/10.1080/09297049.2011.595400.

Stetler, C., & Miller, G. E. (2011). Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosomatic Medicine*, *73*(2), 114–26. http://doi.org/10.1097/PSY.0b013e31820ad12b

Stevens, J. P. (2002). *Applied multivariate statistics for the social sciences* (4th ed.). Mahwah, NJ: LEA.

Sullivan, P. M. S., & Knutson, J. F. (2000). Maltreatment and Disabilities: A Population-Based Epidemioligical Study. *Child Abuse & Neglect*, *24*(10), 1257–1273.

Tabachnick, B. G., & Fidell, L. S. (2001). *Using Multivariate Statistics*. (Allyn and Bacon., Ed.) (4th ed.). Boston.

van der Heijden, K. B., Suurland, J., Swaab, H., & de Sonneville, L. M. J. (2011). Relationship between the number of life events and memory capacity in children. *Child Neuropsychology*, *17*(6), 580–98. http://doi.org/10.1080/09297049.2011.554391

Veiel, H. O. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology*, *19*(4), 587–603. http://doi.org/10.1080/01688639708403745

Vythilingam, M., Heim, C., Ph, D., Newport, J., Miller, A. H., Anderson, E., … Nemeroff, C. B. (2002). Childhood trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry*, *159*(12), 2072–2080.

Wechsler, D. (2008). Wechsler Adult Intelligence Scale–fourth edition (WAIS-IV). In *San Antonio, TX: Psychological Corporation.*

9.2. Studie 2

Cognitive behavioral therapy improves recognition memory in major depression: Results of a randomized controlled trial.

Katharina Dannehl, Winfried Rief, Frank Euteneuer

Division of Clinical Psychology and Psychotherapy, Philipps Universität, Marburg, Germany

Corresponding author: Dr. Frank Euteneuer, Division of Clinical Psychology and Psychotherapy, Philipps Universität, Marburg, Gutenbergstrasse 18, D-35032 Marburg, Germany, Tel: +49 6421 28 23350; Fax: +49 6421 28 28904 . E-mail address: frank.euteneuer@staff.uni-marburg.de

ABSTRACT

Background: Major depression (MD) is associated with deficits in cognitive functioning. Cognitive behavioral therapy (CBT) is a commonly used treatment for depression combining both behavioral activation and cognitive techniques. This study examined whether CBT improves verbal learning and memory in patients with MD. A second aim was to learn whether emphasizing physical exercise during behavioral activation has additional effects on verbal performance.

Methods: Ninety-eight patients with MD were randomly assigned to cognitive behavioral therapy (CBT) emphasizing exercise during behavioral activation (CBT-E), CBT with pleasurable low-energy activities as an active control condition (CBT-C), or a passive waiting list control group (WL). Thirty non-depressed age- and sex-matched controls were included to examine potential verbal learning and memory alterations in MD at baseline. Neuropsychological measures were assessed at baseline and after sixteen weeks of treatment and waiting time respectively.

Results: Patients with MD demonstrated worse cognitive performance than healthy controls in verbal learning, recognition and memory at baseline. When compared to WL, both CBT treatments were associated not only with reduced depressive symptom severity but also with improved recognition memory after treatment. No differences were found between CBT conditions.

Conclusion: Psychological treatments such as CBT can improve recognition memory in MD. These results contradict in part previous assumptions that cognitive impairments persists despite depressive symptom reduction.

Keywords: major depression, cognitive behavioral therapy, cognitive functioning, verbal learning, recognition memory, behavioral activation

Introduction

Major Depressive (MD) is one of the most common mental disorders in the world (World Health Organization, 2008). Besides disturbances in mood and affect, deficits in cognitive functioning such as memory impairment and executive dysfunction have been suggested to be core symptoms in MD (Burt et al., 1995; Hammar et al., 2009; Veiel, 1997; Lee et al., 2012). However, findings on the stability of cognitive deficits in MD are contradictory. Some findings support a trait hypothesis suggesting that cognitive impairment persists despite symptom remission (Hammar et al., 2003; Portella et al., 2003; Neu et al., 2005). In contrast, other findings support a state hypothesis suggesting that cognitive performance improves during remission and recovery from MD (see Austin et al., 2001 and Hasselbalch et al., 2011 for an overview, Biringer et al., 2007; Deuschle et al., 2004).

Cognitive behavioral therapy (CBT) is a well-established treatment for depression (Cuijpers et al., 2013). However, little research has been done on the impact of psychotherapy, in particular CBT, on cognitive functioning in MD and results are ambiguous. As far as we know, only two randomized controlled trials (RCT) have examined the impact of psychotherapy on cognitive functioning. One RCT demonstrated that psychodynamic psychotherapy and its combination with fluoxetine improves cognitive functioning as measured by the Wechsler adult intelligence scale (Bastos et al., 2013). In contrast, a recently published RCT examining the impact of CBT on cognitive performance in MD found no evidence for an improvement in verbal learning and memory, spatial working memory, attention, processing speed and executive functioning (Porter et al., 2016).

Considering that verbal learning and memory might be the most sensitive domains associated with clinical improvement in depression (Douglas et al., 2009), the present RCT examined the impact of CBT on verbal learning and memory performance in patients with MD. CBT mainly consists of two core components: behavioral activation and

cognitive therapy (Dimidjian et al., 2006). When applying behavioral activation, individuals may increase both physical activity and pleasurable experiences. Thus, a further aim of this study was to learn whether the kind of behavioral activation during CBT affects memory outcomes. Considering that physical activity may improve cognitive performance (Chang et al., 2011; Chang, et al., 2012; Colcombe et al., 2003; Smith et al., 2011), we hypothesized that CBT that emphasizes exercise has additional beneficial effects on verbal performance.

Method

Participants

This randomized controlled trial was conducted from August 2011 to February 2015 with German Psychological Society Review Board approval. The study was part of the Outcome of Psychological Interventions in Depression (OPID) -trial. OPID is an ongoing research project that aims to improve outcomes in treatment for Major Depression. OPID involves four different arms: i) cognitive-behavioral therapy with exercise (CBT-E), ii) an active control condition for CBT-E, including CBT with pleasurable low-energy activities (CBT-C), iii) Cognitive Behavioral Analysis Ssystem of Psychotherapy, and iv) a passive waitlist control condition (WL). Arms i-iii also captured a neuropsychological evaluation and were funded as a separate subproject by the German Research Foundation from 2011–-2015 (DFG RI 574/23-1/SCHE 341/20-1). Ninety-eight patients aged 18-65 who fulfilled criteria for MD in DSM-IV (Wittchen et al., 1997) and who were randomly assigned using simple computerized randomization to either CBT-E, CBT-C, or WL were analyzed. A sample of 30 age- and sex-matched healthy controls from the same community was studied to examine potential baseline alterations in cognitive functioning in MD. Patients were recruited via the Outpatient Clinic for Psychological Interventions of the University of

Marburg, via advertisements, leaflets in pharmacies and waiting rooms of doctors, as well as press releases in local newspapers. Healthy controls were recruited via advertisements and press releases in local newspapers. After prescreening via phone, participants underwent a diagnostic session which included the German version of the structured clinical interview for DSM-IV (Wittchen et al., 1997) and an interview that focused on exclusion criteria and socio-demographic variables. Exclusion criteria were neurological illness, psychotic symptoms, injuries during the last 2 weeks, alcohol and/or drug abuse, antipsychotics, stimulants, current pregnancy and lactation in women and any mental disorders according to DSM-IV for the healthy controls. Patients who took antidepressants were considered for participation under the assumption that the dose had been stable for at least 2 weeks and would remain so during study participation.

Interventions

Both CBT treatments (i.e., CBT-E and CBT-C) were based on a common CBT manual and structured through phases typically used in CBT (Hautzinger et al., 2003). Patients participated in 50 minutes individual manualized psychotherapy weekly for 16 weeks. All therapists were clinical psychologists with advanced or completed postgraduate clinical training in CBT. Patients and therapists were blinded to the purpose and study hypothesis. After an initial phase (Weeks 1-4), patients received behavioral activation (Weeks 5-9) with either exercise (CBT-E) or pleasant low-energy activities in the active control condition (CBT-C), followed by cognitive therapy (Weeks 10-16).

For CBT-E, CBT was modified to increase physical activity according to the recommendations of the World Health Organization ("World Health Organization, Global Recommendations on Physical Activity for Health, WHO Press, Geneva, Switzerland," 2010). During the initial phase, patients received psychoeducation on MD and on the rela-

tionship between thoughts, feelings, and behavior, with a focus on physical activity as a health behavior potentially relevant for depressive symptoms (Craft et al., 2004; Roshanaei-Moghaddam et al., 2009). Psychoeducation further addressed recommendations for being physically active (Craft et al., 2004; "World Health Organization, Global Recommendations on Physical Activity for Health, WHO Press, Geneva, Switzerland," 2010). Additional elements were case conceptualization (i.e., assessment of individual risk factors for depression) and, if necessary, problem-solving strategies were applied to reduce barriers to being physical active (e.g. coping with low social support, arranging options for exercise). Patients received a manual summarizing the content of psychoeducation and providing a list of potential physical activities (e.g. walking, jogging, swimming, gyms), as well as physical activity dose recommendations based on the Ainsworth Compendium of Physical Activities (Ainsworth et al., 1993). These issues were discussed within treatment sessions and used to prepare an individualized schedule with at least four 40-minutes homework exercise sessions per week consisting of at least moderate physical activity. During the phase of behavioral activation, the schedule was applied and common behavioral activation techniques were used to assist patients (e.g., reinforcement, activity and mood monitoring, problem solving). After the phase of behavioral activation, therapists recommended patients to continue physical activity but shifted their focus to cognitive aspects, such as modification of dysfunctional cognitions and beliefs, enhancement of cognitions that increase psychological well-being, as well as prevention of relapse (Hautzinger et al., 2003).

The second condition (i.e., CBT-C) involved CBT with behavioral activation emphasizing pleasurable experiences without a substantial increase in physical activity (i.e., euthymic activities). Different from CBT-E, patients received psychoeducation on MD and on the relationship between thoughts, feelings and behavior with a focus on euthymic ac-

tivities. The euthymic activities were based on a manual for euthymic therapy, an intervention for mental disorders that shares similarities with mindfulness therapy (Lutz, 2005). Analogous to CBT-E, the activity schedule within behavioral activation involved at least four 40-minutes homework sessions per week including euthymic exercises that bring awareness to different senses such as hearing (e.g. listening to music), tasting (e.g. preparing and enjoying a meal), smelling (e.g. taking a scented bath) or touching (e.g. bringing attention to the sensations of skin contact with pleasant surfaces) (Lutz, 2005). After the phase of behavioral activation, therapists also recommended patients to perform euthymic activities autonomously and shifted the focus to cognitive therapy similar to CBT-E. Patients in the WL condition (i.e., passive control condition) did not receive any treatment but were involved in regular psychotherapy after their 16-weeks waiting time.

Depressive symptoms and physical activity

Depressive symptoms were assessed with the German version of the Beck Depression Inventory-II (BDI, Hautzinger et al., 2006). Metabolic equivalent minutes per week (MET-min/wk) were analyzed for moderate-intensity and vigorous-intensity activity using the long version of the International Physical Activity Questionnaire (IPAQ; Craig et al., 2003)

Neuropsychological assessment

To measure verbal learning and memory, the German adaptation of the "Rey auditory Verbal Learning Test" (VLMT, Helmstaedter et al., 2001) was used. The VLMT requires the learning and immediate recall of a list of 15 items during five learning trials, one-time presentation and immediate free recall of a distractor list of the same length, free recall of

the items after distraction, free recall after a filled retention interval (about 20 min) and delayed yes–no recognition. The total number of items reproduced after Trial 1 and after Trial 5 as well as the sum of words reproduced in Trial 1-5, the reproduced distractor words, the reproduced words after delay (Trial 7) and the number of correctly recognized words during yes-no recognition (recognition list) were measured. Neuropsychological tests were conducted at the beginning (T1; before the first session) and at the end of the treatment (T2; after the last session). All participants were tested between 7:00 am and 10:00 am.

Statistical analysis

The statistical analyses were carried out with SPSS version 23.0 for Windows (Chicago, SPSS, Inc.). Baseline differences in group characteristics were calculated with t-tests, analysis of variance and chi square tests as appropriate. Intervention effects on outcomes with more than one follow-up measure point (i.e., depressive symptoms and physical activity) were analyzed with multilevel models, while intervention effects on outcomes with only one follow-up measure point (i.e., neuropsychological assessment) were analyzed with analysis of covariance to increase statistical power (Twisk et al., 2008; Van Breukelen, 2006). Analyses were performed on an intention-to-treat base using full information maximum likelihood (FIML) estimation for multilevel models and multiple imputation for analyses of covariance. Multilevel models were tested with different covariance structures, and for each model, the covariance structure which provided the smallest Akaike information criterion (and typically the smallest Bayesian information criterion as well) was selected (Akaike, 1974). For analyses of covariance, five imputed data sets were created followed by five independent analyses. Imputations were based on all variables

from Table 1, treatment allocation, and on primary and secondary outcomes. Data from 98 randomized participants were analyzed.

Results

Baseline characteristics

Descriptive statistics for all groups and comparisons between patients with MD and age- and sex-matched healthy controls are presented in table 1. Patients with MD demonstrated worse cognitive performance than healthy controls in memory, as revealed by the performance in trial 5 of the VLMT, (F (1, 118) =-2.9, p = 0.005), the overall performance (trial 1-5) (F (1, 118) = -2.8, p = 0.007), the performance after a 20 min. delay (F (1, 116) = -2.4, p = 0.020) and the ability to recognize words (F (1, 117) = -2.7, p = 0.009). No significant differences were assessed for reproducing trial 1 and the distractor list.

Neuropsychological outcomes

Analysis of covariance revealed a significant effect of the treatment group on recognition performance, (F (2, 85) = 5.42, p = 0.012), (Figure 2). Compared to the WL condition, patients´ performance in the recognition memory task was better when receiving 16 weeks of both CBT-E, (t (85) = 2.99, p =0.005) and CBT-C, (t (85) = 2.64, p = 0.022). No significant differences were observed between CBT-E and CBT-C (p = 0.656). Treatment groups did not significantly differ in other verbal learning and memory outcome measures (p = 0.294 - 0.519).

Depression and physical activity outcomes

The pattern of change over time between the three groups was statistically significant for depressive symptoms (group x time: F (4, 81.3) = 6.27; p = < 0.001). As compared with

WL, CBT-E resulted in significantly lower depressive symptoms at week 16 (t (86.9) = 2.90; p = 0.005), CBT-C also resulted in lower depressive symptoms at week 16 (t (83.0) = 3.16; p = 0.003). CBT-E and CBT-C did not differ significantly in depressive symptoms at week 16 (t (86.5) = -0.14; p =0.889).

Change in vigorous-intensity activity between groups was statistically significant (group x time: F (4, 78.7) = 3.25; p = 0.016). As compared to WL, CBT-E was associated with higher levels of vigorous-intensity activity at week 8 (t (90.4) = -2.00; p = 0.049) with non-significant differences at week 16 (t (78.3) = -1.51; p = 0.136). As compared to CBT-C, CBT-E was related with higher levels of vigorous-intensity activity at week 8 (t (72.9) = -2.74; p = 0.008), and a trend for higher levels at week 16 (t (78.4) = -1.80; P = 0.075). WL and CBT-C resulted in no statistically significant difference in vigorous-intensity activity at week 8 (t (90.0) = 0.12; p = 0.907) and 16 (t (76.7) = 0.25; p = 0.801). There were no statistically significant group x time interactions on moderate-intensity activity (p = 0.499).

Discussion

This study examined the impact of CBT on verbal learning and memory in patients with MD. A further aim was to learn whether the type of behavioral activation during CBT (i.e., exercise versus pleasurable low-energy activities) affects neuropsychological outcomes. In line with previous research, the present study showed impaired verbal learning abilities and memory in patients with MD (Lee et al., 2012; Porter et al., 2003). Sixteen weeks of treatment with CBT were not only associated with reduced depressive symptom severity but also with improved recognition memory. This effect was independent of the kind of behavioral activation within CBT.

In light of the influence of cognitive impairment on aspects of general functioning (i.e., quality of life, daily living activities or employment status) (Bortolato et al. 2014), research targeting the improvement of cognitive functioning is required. Our findings indicate that interventions for depression can, in part, reverse impairments in cognitive performance. This observation is novel in the context of CBT and contradicts findings from a recently published study that found no evidence for an effect of CBT on cognitive functions in MD (Porter et al., 2016). Importantly, improvement in verbal performance in MD has also been found in trials with antidepressants. Corresponding with the assumption that the sensitivity to changes is high for verbal learning and memory (Douglas et al., 2009; Douglas et al., 2011), Herrera-Guzmán et al. demonstrated a large increase in verbal and visual memory, and to a lesser degree in the working memory and mental processing speed after treatment with antidepressants (Herrera-Guzmán et al., 2009). Likewise, Biringer et al. found improved verbal memory function after treatment with antidepressants, while no significant improvements were found for other dimensions of neurocognitive function (Biringer et al., 2007). A recently published exploratory study complements these findings and shows an improvement of performance in spatial working memory and attention after treatment with metacognitive therapy (MCT) and CBT, with slight advantage of MCT (Groves et al., 2015). In our study, recognition memory improved significantly compared to the passive control condition. Prior research suggested that free recall and recognition make different demands on a subject's resources (Brand et al., 1992). Free recall might be more effortful, whereas recognition seems to be a more passive process. One could assume that less demanding processes, like recognition, might be easier to modify and are more sensitive to changes in the clinical status of patients with MD.

This study has limitations. Our sample consisted of outpatients with MD who were eligible for psychological treatment. Thus, findings may not generalize to other samples of

patients (e.g., MD patients with psychotic features). Second, our study design allows no conclusions about the specific efficacy of behavioral activation or cognitive aspects or the combination of both within CBT. Future research should address this issue.

In conclusion, this study found evidence for a beneficial impact of psychotherapy on verbal recognition memory. The treatment with CBT may offer not only a successful way to reduce depressive symptoms but also provide a possibility to influence cognitive impairment in major depression.

Acknowledgements:

Conflict of interest
None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Role of funding source

This study was funded by a grant from the German Research Foundation (DFG) to Dr. Rief (Ri 574/23-1). The DFG had no further role in the study's design or in collecting, analyzing or interpreting study data nor in writing the report or in the decision to submit the paper for publication. ClinicalTrials.gov Identifier: NCT01464463 (The Impact of Psychological Interventions on Psychometric and Immunological Measures in Patients with Major Depression).

Table 1. Sociodemographic characteristics, psychopathological measures and cognitive test scores at baseline.

Variable	MD, CBT-E (n = 34)	MD, CBT-C (n = 34)	MD, WL (n = 30)	MD, Total (n = 98)	HC (n = 30)	t or $\chi 2$; p
Age	36.9 (10.8)	37.2 (12.5)	37.9 (13.5)	37.3 (12.2)	37.1 (12.2)	0.08; .939
Female, Number (%)	16 (47.1)	19 (55.9)	13 (43.3)	48 (49.0)	15 (50.0)	.01; .922
Depressive symptom severity, BDI-II	27.0 (9.1)	27.3 (8.7)	26.2 (9.9)	26.9 (9.1)	4.6 (5.5)	18.26; <.001
DSM-IV Axis I comorbidity, Number (%)						
Anxiety disorders	8 (23.5)	7 (20.6)	8 (26.7)	23 (23.5)	0 (0.0)	8.58; .003
Somatoform disorders	2 (5.9)	4 (11.8)	6 (20.0)	12 (12.2)	0 (0.0)	4.05; .044
Body mass index, kg/m^2	25.8 (4.1)	26.2 (6.3)	26.5 (5.7)	26.1 (5.3)	24.0 (4.2)	1.96; .052
Education (Years)	11.5 (1.7)	11.3 (1.7)	11.0 (1.7)	11.3 (1.7)	12.2 (1.5)	-2.83; .006
Number of cigarettes/day	3.5 (7.3)	1.5 (4.8)	4.2 (8.8)	3.0 (7.1)	0.5 (1.9)	1.90; .060
Antidepressant medication, Number (%)	14 (41.2)	13 (38.2)	10 (33.3)	37 (37.8)	0 (0.0)	15.93; <.001
Physical activity, IPAQ, MET-minutes/week						
Moderate-intensity activity	1817.7 (2321.0)	2441.9 (2321.3)	1842.5 (1884.8)	2040.0 (2227.0)	2243.8 (2813.1)	-0.87; .388
Vigorous-intensity activity	917.5 (1561.1)	898.2 (1574.4)	760.0 (1921.1)	861.1 (1670.6)	1577.3 (1739.28)	-2.03; .045
Verbal learning and memory (VLMT)						
Trial 1, no. of words	6.8 (2.5)	7.2 (2.6)	6.6 (2.6)	6.9 (2.6)	7.9 (2.2)	-1.9; .060
Trial 5, no. of words	12.3 (2.2)	12.2 (3.3)	11.9 (1.8)	12.1 (2.5)	13.3 (1.6)	-2.9; .005
Total trial 1–5, sum of words	50.7 (12.1)	53.2 (13.2)	49.6 (10.4)	51.3 (11.9)	56.7 (8.0)	-2.8; .007
Distracter list, no. of words	5.8 (1.9)	6.1 (2.2)	5.8 (1.7)	5.9 (1.9)	6.6 (2.3)	-1.7; .090
Trial 7 – after delay, no. of words	10.7 (3.1)	11.4 (4.3)	9.1 (7.8)	10.5 (3.8)	12.0 (2.8)	-2.4; .020
Recognition list	14.1 (1.0)	14.0 (1.9)	13.7 (1.7)	13.9 (1.6)	14.5 (0.7)	-2.7; .009

Values are mean (SD) unless noted with percentage. Group differences were calculated using χ^2 tests for categorical variables and analyses of variance or t-tests for continues variables. BDI, Beck Depression Inventory; VLMT = Verbal Learning and Memory Test; CBT-E, Cognitive-behavioral therapy with physical activity; CBT-C, Cognitive-behavioral therapy with euthymic activity; DSM, Diagnostic and Statistical Manual of Mental Disorders; HC, healthy control group; IPAQ, International Physical Activity Questionnaire; MD, Major Depression; MET, metabolic equivalent; WL, wait list control group.

Table 2.

Means and Standard Deviations (in Parentheses) of Outcomes at Baseline, Mid-treatment and Post-treatment

	Baseline	Week 8 post-behavioral activation	Week 16 post-treatment
Depressive symptom severity, BDI-II			
CBT-E	27.0 (9.1)	18.4 (10.7)	14.6 (13.5)
CBT-C	27.3 (8.7)	19.1 (9.5)	14.8 (11.4)
WL	26.2 (9.9)	29.5 (12.1)	23.5 (11.0)
Moderate-intensity activity, MET-minutes/week			
CBT-E	1817.7 (2321.0)	1981.5 (2667.4)	2396.5 (3812.8)
CBT-C	2441.9 (2321.3)	1437.3 (1997.6)	1996.5 (2624.8)
WL	1842.5 (1884.8)	1620.0 (1538.2)	1712.3 (1751.8)
Vigorous-intensity activity, MET-minutes/week			
CBT-E	917.5 (1561.1)	1640.0 (2137.9)	1669.6 (2815.2)
CBT-C	898.2 (1574.4)	549.7 (1153.3)	714.6 (1287.9)
WL	760.0 (1921.1)	565.7 (786.0)	692.3 (1483.1)
Verbal learning and memory (VLMT)			
Trial 1, no. of words			
CBT-E	6.8 (2.5)	-	8.1 (2.6)
CBT-C	7.2 (2.6)	-	8.0 (2.6)
WL	6.6 (2.6)	-	7.5 (2.1)

Trail 5, no of words			
CBT-E	12.3 (2.2)	-	12.8 (2.1)
CBT-C	12.2 (3.3)	-	13.1 (1.9)
WL	11.9 (1.8)	-	12.3 (2.7)
Trail 1-5, sum of words			
CBT-E	50.7 (12.1)	-	55.5 (11.2)
CBT-C	53.2 (13.2)	-	57.0 (9.4)
WL	49.6 (10.4)	-	52.6 (9.8)
Distractor list, no. of words			
CBT-E	5.8 (1.9)	-	6.5 (2.2)
CBT-C	6.1 (2.2)	-	7.6 (3.1)
WL	5.8 (1.7)	-	6.1 (2.3)
Trial 7- after delay, no. of words			
CBT-E	10.7 (3.1)	-	11.1 (3.2)
CBT-C	11.4 (4.3)	-	11.9 (2.9)
WL	9.1 (7.8)	-	10.0 (3.6)
Recognition, no. of words			
CBT-E	14.1 (1.0)	-	14.4 (0.9)
CBT-C	14.0 (1.9)	-	14.5 (0.8)
WL	13.7 (1.7)	-	13.5 (1.9)

Note. BDI = Beck Depression Inventory; VLMT = Verbal Learning and Memory Test; CBT-E = Cognitive-behavioral therapy with exercise; CBT-C = Cognitive-behavioral therapy with euthymic activity; MET = metabolic equivalent; WL = wait list control group.

Figure 1

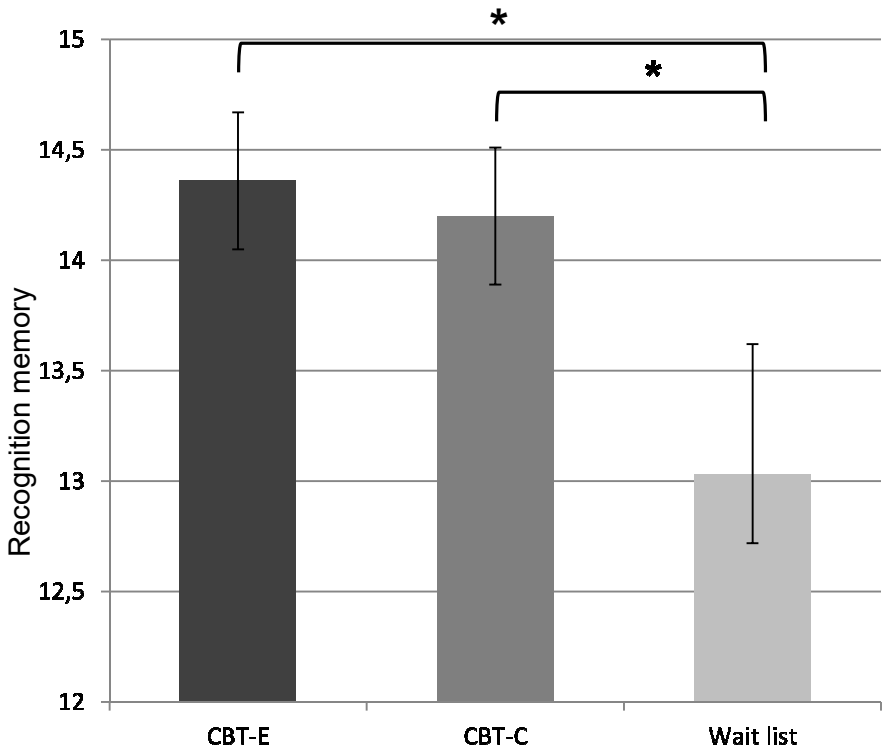

Figure 1.

Recognition memory at week 16 (Post-treatment) by treatment group adjusted for baseline values. Values are estimated marginal means (SEM) from analysis of covariance. Cognitive behavioral therapy with exercise (CBT-E) versus waitlist (WL, passive control condition) and cognitive behavioral therapy with pleasurable low-energy activities (CBT-C) versus waitlist (WL, passive control condition):* $P<0.05$.

References

Ainsworth, B. E., Haskell, W. L., Leon, A. S., Jacobs, D. R., Montoye, H. J., Sallis, J. F., & Paffenbarger, R. S. (1993). Compendium of physical activities: classification of energy costs of human physical activities. *Medicine and Science in Sports and Exercise*, *25*(1), 71–80.

Akaike, H. A. (1974). A new look at the statistical model identification. *IEEE Trans Automat Contr.*, *19*(6), 716–723.

Bastos, A. G., Pinto Guimarães, L. S., & Trentini, C. M. (2013). Neurocognitive changes in depressed patients in psychodynamic psychotherapy, therapy with fluoxetine and combination therapy. *Journal of Affective Disorders*, *151*(3), 1066–1075.

Biringer, E., Mykletun, A., Sundet, K., Kroken, R., Stordal, K. I., & Lund, A. (2007). A longitudinal analysis of neurocognitive function in unipolar depression. *Journal of Clinical and Experimental Neuropsychology*, *29*(8), 879–91.

Brand, A. N., Jolles, J., & Gispen-de Wied, C. (1992). Recall and recognition memory deficits in depression. *Journal of Affective Disorders*, *25*(1), 77–86.

Bortolato, B., Carvalho, A. F., & McIntyre, R. S. (2014). Cognitive Dysfunction in Major Depressive Disorder: A State-of-the-Art Clinical Review. *CNS & Neurological Disorders-Drug Targets*, *13*(10), 1804–1818.

Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin*, *117*(2), 285–305.

Chang, Y.-K., Tsai, C.-L., Hung, T. M., So, E. C., Chen, F. T., & Etnier, J. L. (2011). Effects of acute exercise on executive function: a study with a Tower of London Task. *Journal of Sport & Exercise Psychology*, *33*(6), 847–865.

Chang, Y.-K., Tsai, C.-L., Labban, J., Gapin, J., & Etnier, J. L. (2012). The effects of acute

exercise on cognitive performance: A meta-analysis. *Brain Research*, *1470*, 1–15.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults. *Psychological Science*, *14*, 125.

Craft, L. L., & Perna, F. M. (2004). The benefits of exercise for the clinically depressed. *Primary Care Companion to the Journal of Clinical Psychiatry*, *6*(3), 104–111. Journal Article.

Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., … Oja, P. (2003). International physical activity questionnaire: 12-Country reliability and validity. *Medicine and Science in Sports and Exercise*, *35*(8), 1381–1395.

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, *58*(7), 376–85.

Deuschle, M., Kniest, A., Niemann, H., Erb-Bies, N., Colla, M., Hamann, B., & Heuser, I. (2004). Impaired declarative memory in depressed patients is slow to recover: Clinical experience. *Pharmacopsychiatry*, *37*(4), 147–151.

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., Addis, M. E., … Jacobson, N. S. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology*, *74*(4), 658–70.

Douglas, K. M., & Porter, R. J. (2009). Longitudinal assessment of neuropsychological function in major depression. *The Australian and New Zealand Journal of Psychiatry*, *43*(12), 1105–1117.

Douglas, K. M., Porter, R. J., Knight, R. G., & Maruff, P. (2011). Neuropsychological

changes and treatment response in severe depression. *The British Journal of Psychiatry : The Journal of Mental Science*, *198*(2), 115–122.

Groves, S. J., Porter, R. J., Jordan, J., Knight, R., Carter, J. D., McIntosh, V. V. W., … Joyce, P. R. (2015). Changes in neuropsychological function after treatment with metacognitive therapy or cognitive behavior therapy for depression. *Depression and Anxiety*, *32*(6), 437–444.

Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: A systematic review. *Journal of Affective Disorders*, *134*(1–3), 20–31.

Hautzinger, M. (2003). Kognitive Verhaltenstherapie bei Depressionen. *Weinheim: Psychologie Verlags Union*.

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Beck Depressions-Inventar (BDI-II). Revision. Harcourt Test Services.*

Helmstaedter, C., Lendt, M., & Lux, S. (2001). VLMT Verbaler Lern- und Merkfähigkeitstest. *Göttingen: Beltz Test GmbH*.

Herrera-Guzmán, I., Gudayol-Ferré, E., Herrera-Guzmán, D., Guàrdia-Olmos, J., Hinojosa-Calvo, E., & Herrera-Abarca, J. E. (2009). Effects of selective serotonin reuptake and dual serotonergic-noradrenergic reuptake treatments on memory and mental processing speed in patients with major depressive disorder. *Journal of Psychiatric Research*, *43*(9), 855–863.

Lee, R. S. C., Hermens, D. F., Porter, M. a, & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of Affective Disorders*, *140*(2), 113–24.

Lutz, R. (2005). The therapeutic concept of euthymic treatment. The little school of pleasure. *MMW Fortschr Med.*, *147*(37), 41–3.

Neu, P., Bajbouj, M., Schilling, A., Godemann, F., Berman, R. M., & Schlattmann, P. (2005). Cognitive function over the treatment course of depression in middle-aged patients: Correlation with brain MRI signal hyperintensities. *Journal of Psychiatric Research*, *39*(2), 129–135.

Portella, M. J., Marcos, T., Rami, L., Navarro, V., Gastó, C., & Salamero, M. (2003). Residual cognitive impairment in late-life depression after a 12-month period follow-up. *International Journal of Geriatric Psychiatry*, *18*(7), 571–576.

Porter, R. J. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *The British Journal of Psychiatry*, *182*, 214–220.

Porter, R. J., Bourke, C., Carter, J. D., Douglas, K. M., McIntosh, V. V. W., Jordan, J., … Frampton, C. M. A. (2016). No change in neuropsychological dysfunction or emotional processing during treatment of major depression with cognitive-behaviour therapy or schema therapy. *Psychological Medicine*, *46*(2), 393–404.

Roshanaei-Moghaddam, B., Katon, W. J., & Russo, J. (2009). The longitudinal effects of depression on physical activity. *General Hospital Psychiatry*, *31*(4), 306–15.

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Strauman, T. A., Welsh-bohmer, K., Jeffrey, N., & Sherwood, A. (2011). Aerobic Exercise and Neurocognitive Performance: a Meta-Analytic Review of Randomized Cortrolled Trials. *Psychoso*, *72*(3), 239–252.

Snyder, H. R. (2014). Major Depressive Disorder is Associated with Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review. *Psychological Bulletin*, *139*(1), 81–132.

Twisk, J. W. R., & de Vente, W. (2008). The analysis of randomised controlled trial data with more than one follow-up measurement. A comparison between different approaches. *European Journal of Epidemiology*, *23*(10), 655–60.

Van Breukelen, G. J. P. (2006). ANCOVA versus change from baseline had more power in randomized studies and more bias in nonrandomized studies. *Journal of Clinical Epidemiology*, *59*(9), 920–925.

Veiel, H. O. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology*, *19*(4), 587–603.

Wittchen, H.-U., Wunderlich, U., Gruschitz, S., & Zaudig, M. (1997). *Strukturiertes Klinisches Interview für DSM-IV, Achse I (SKID-I). Göttingen: Hogrefe.*

World Health Organization, Global Recommendations on Physical Activity for Health, WHO Press, Geneva, Switzerland. (2010).

9.3. Studie 3

Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

The predictive value of somatic and cognitive depressive symptoms for cytokine changes in patients with major depression

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
28 June 2014
Number of times this article has been viewed

Katharina Dannehl[1]
Winfried Rief[1]
Markus J Schwarz[2]
Annika Hennings[1]
Sabine Riemer[1]
Verena Selberdinger[3]
Theresa Stapf[3]
Frank Euteneuer[1]

[1]Division of Clinical Psychology and Psychotherapy, Philipps Universität Marburg, Marburg, Germany; [2]Institute for Laboratory Medicine, Ludwig-Maximilian Universität, Munich, Germany; [3]Department of Psychiatry, Ludwig-Maximilian Universität, Munich, Germany

Context: Elevated concentrations of proinflammatory cytokines have been hypothesized as an important factor in the pathophysiology of depression. Depression itself is considered to be a heterogeneous disorder. Current findings suggest that "cognitive" and "somatic" symptom dimensions are related to immune function in different ways. So far, little research has been done on the longitudinal aspects of inflammation in patients with major depression, especially with respect to different symptom dimensions of depression. Therefore, we investigated which aspects of depression may predict changes in tumor necrosis factor-alpha (TNF-alpha) and interleukin (IL)-6 over 4 weeks.

Methods: Forty-one patients with major depression diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), and 45 healthy controls were enrolled. Serum measurements of TNF-alpha and IL-6 were conducted at baseline and 4 weeks later. Psychometric measures included the assessment of cognitive-affective depressive symptoms and somatic symptoms during the last 7 days as well as somatic symptoms during the last 2 years.

Results: Patients with depression showed increased levels of TNF-alpha ($P<0.05$) compared to healthy controls. Hierarchical regression analyses indicated that neither depressive nor somatic symptoms predict changes in proinflammatory cytokines in the whole sample of depressed patients. Moderation analyses and subsequent sex-stratified regression analyses indicated that higher somatoform symptoms during the last 2 years significantly predict an increase in TNF-alpha in women with major depression ($P<0.05$) but not in men. Exploratory analyses indicated that the stability of TNF-alpha and IL-6 (as indicated by intraclass correlation coefficients) over 4 weeks was high for TNF-alpha but lower for IL-6.

Conclusion: The present study demonstrated that a history of somatoform symptoms may be important for predicting future changes in TNF-alpha in women with major depression.

Keywords: interleukin-6, tumor necrosis factor-alpha, symptom dimension

Introduction

Elevated concentrations of cytokines have been hypothesized as an important factor in the pathophysiology of depression. Meta-analytic results indicate increased levels of the proinflammatory cytokines interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-alpha) in depressed patients compared to healthy controls.[1,2] A recent study with healthy individuals has shown that depressive symptoms may precede and augment some inflammatory processes.[3] Inflammatory mechanisms have been suggested to play a pivotal role in the relationship between depression and cardiovascular disease.[4,5]

Depression itself is considered to be a heterogeneous disorder. Current findings suggest that "cognitive" and "somatic" symptom dimensions are related in different ways

Correspondence: Katharina Dannehl
Division of Clinical Psychology and Psychotherapy, Philipp University of Marburg, Gutenbergstrasse 18, Marburg, Germany
Tel +49 6421 282 3347
Fax +49 6421 282 8904
Email dannehl@staff.uni-marburg.de

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/NDT.S61640

to immune function and cardiovascular outcomes. Somatic symptoms have been shown to be better predictors of cardiovascular mortality and cardiac events in post-myocardial infarction patients and in patients with chronic heart failure (CHF).[6–10] Additionally, somatic but not cognitive-affective depressive symptoms have been related to cardiovascular risk factors such as decreased heart rate variability and reduced baroreflex sensitivity.[11,12] Somatic symptoms (especially sleeping disorders) predict further depressive episodes better than cognitive-affective symptoms.[13] Regarding immunological measures, Duivis et al demonstrated that somatic symptoms of depression and anxiety but not cognitive symptoms are associated with higher inflammatory levels of C-reactive protein (CRP), IL-6, and TNF-alpha in a population-based sample.[14] In patients with major depression, increased levels of soluble interleukin-2 receptors (sIL-2R) were associated with higher severity ratings of somatic symptoms but not with cognitive-affective depressive symptoms.[15]

Though many studies have focused on cross-sectional relationships between depression and proinflammatory cytokines, little research has been done on longitudinal aspects of inflammation in patients with major depression, especially with respect to different symptom dimensions of depression.[16] In the present investigation, we aimed to learn whether changes in IL-6 and TNF-alpha over 1 month can be predicted by measures of cognitive-affective and somatic symptoms in patients with major depression. The prediction of changes in these inflammatory markers may be of relevance because an increase of proinflammatory cytokines contributes to several poor health outcomes.[17–20] We hypothesized that primarily somatic aspects of depression may predict an increase in proinflammatory cytokines. Since previous research indicates sex differences in depression, immune function, and symptom dimensions, we further focused on the moderating role of sex.[21–23] All analyses were performed for the whole sample and separated by sex.

Methods

Subjects

The study was approved by the ethics committees of the German Psychological Society and the Institutional Review Board of Munich University Clinical Center. Forty-one outpatients with major depression were recruited from the Outpatient Clinic for Psychological Interventions of the University of Marburg and the Department of Psychiatry of Munich University. Furthermore, 45 healthy controls were enrolled in the study. All participants underwent a diagnostic session which included the German version of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (SCID for the DSM-IV)[24] and an interview that focused on exclusion criteria and on demographic variables. Exclusion criteria were organic illnesses involving the central nervous system (CNS) or affecting immune status (inflammatory diseases, infections, injuries in the last 2 weeks), psychotic symptoms, somatization disorder, pain disorder, alcohol and/or drug abuse, antipsychotics, stimulants, current psychotherapy (to allow reliable and unbiased evaluation of psychopathology), pregnancy and lactation in women, and any psychiatric diagnosis according to DSM-IV in controls.

Procedures

Participants visited the research facility for measurements at baseline (T1) and 4 weeks later (T2), without any intervention in the meantime. Most of these patients were considered for further ongoing longitudinal research after participating in the present investigation. Depressive and somatic symptoms as well as biological parameters were assessed at each visit.

Measures

Psychological variables

As mentioned in Methods, the German version of the SCID[24] was used to confirm the diagnosis of major depression and comorbid axis-I disorders. The symptom severity of each participant was assessed using the German version of the Beck Depression Inventory II (BDI II).[25] Cognitive-affective symptoms were assessed using the cognitive-affective subscale of the BDI II. To measure somatic symptom dimensions, two screenings for somatoform symptoms were used.[26] The Screening for Somatoform Symptoms Scale-7 (SOMS-7) consists of 53 items, and measures somatic symptoms listed for somatization disorder and somatoform autonomic dysfunction in DSM-IV and the International Classification of Diseases, tenth revision (ICD-10) for the last 7 days. The Screening for Somatoform Symptoms Scale-2 (SOMS-2) included 68 items and rates somatic symptoms for the last 2 years. Both scales usually included six sex-related items, which were excluded to assure a better comparability between female and male participants.

Cytokine analysis

Blood samples were collected at 8 am, centrifuged, and stored at –80°C until thawed for assay. Participants were instructed to avoid exercise and alcohol 24 hours prior to blood withdrawal. Also, participants were instructed to avoid rushing and taking public transportation to the laboratory to

avoid physical overexertion before blood sampling. Serum concentrations of IL-6 and TNF-alpha were determined using highly sensitive immunoassays according to the manufacturer's instructions (Human IL-6 Quantikine HS and Human TNF-alpha Quantikine HS; R & D Systems, Minneapolis, MN, USA).

Statistical analysis

The statistical analyses were carried out with SPSS software (v19.0 for Windows; IBM Corporation, Armonk, NY, USA). As the immunological parameters were not normally distributed, the values of inflammatory markers were log-transformed to allow parametric testing. Boxplots were used to control for univariate outliers. Screening for multivariate outliers was performed by calculating Studentized deleted residuals and centered leverage values.[27] To test for mean differences of cytokines and psychometric variables between patients and healthy controls, data were analyzed by repeated measures analysis of variance (ANOVA). In the same way, interaction effects of group, sex, and time were calculated. Pearson product-moment correlations were calculated to examine the relationships between cytokines and psychometric measures (BDI II, BDI II subscale, SOMS-7, SOMS-2) at baseline measurement (T1). To examine prospective relationships between depressive and somatic symptoms and changes in proinflammatory cytokines, hierarchical regression analyses were conducted. Baseline levels of cytokines were entered at step 1 while symptom dimensions were entered at step 2 to predict cytokine levels 4 weeks later. A number of moderation analyses were carried out to measure possible interactions between sex and symptom dimension in the prediction of changes in cytokines. Pearson product-moment correlation coefficients were used to examine the relationship between changes in psychometric measurements and changes in cytokine levels. Exploratory analyses of intraclass correlation coefficients (ICC) were conducted to estimate the variability of cytokine levels over time and 95% confidence intervals were calculated.

Results

The characteristics of participants and group differences in study variables are presented in Table 1. Patients with major depression and controls did not differ significantly with respect to age, education, sex, body mass index

Table 1 Characteristics of patients with MD and HC

	MD (n=41)	HC (n=45)	P-value
Sociodemographic data			
Age	33.2 (12.52)	36.5 (13.19)	0.220
Sex: female, n (%)	23.0 (60)	29.0 (64.7)	0.710
Years of education	12.38 (1.33)	12.61 (1.1)	0.363
Body mass index, kg/m²	25.10 (5.0)	24.05 (5.5)	0.360
Use of antidepressives: yes (%)	8 (19.51)	–	
Current smoker, n (%)	16 (39.02)	16 (35.56)	0.392
DSM-IV comorbidity, n (%)			
Undifferentiated somatization	3 (7.32)	–	
Panic disorder	6 (14.63)	–	
Generalized anxiety disorder	2 (4.88)	–	
Post-traumatic stress disorder	5 (12.2)	–	
Social phobia	7 (17.07)	–	
Specific phobia	2 (4.88)	–	
Body dysmorphic disorder	1 (2.44)	–	
Eating disorder	2 (4.88)	–	
Obsessive compulsive disorder	1 (2.44)	–	
Psychopathological measures			
BDI II	22.3 (10.37)	3.06 (4.25)	0.000
Cognitive-affective symptoms subscale, BDI II	8.5 (4.5)	0.9 (1.4)	0.000
Somatoform symptoms severity index, SOMS-7	23.05 (19.52)	6.08 (6.03)	0.000
Somatoform symptoms severity index, SOMS-2	15.24 (9.67)	4.25 (5.65)	0.000
Cytokines, pg/mL			
Tumor necrosis factor-alpha	1.41 (0.43)	1.12 (0.42)	0.039
Interleukin-6	1.19 (0.72)	1.14 (0.73)	0.288

Notes: Group differences were calculated by repeated measures analysis of variance and chi-square tests as appropriate. Values shown as mean (SD) unless otherwise noted. Cytokine analyses were executed using log-transformed data (non-transformed data are shown to facilitate interpretation).
Abbreviations: BDI II, Becks Depression Inventory II; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; HC, healthy controls; MD, major depression; SD, standard deviation; SOMS, Screening for Somatoform Symptoms Scale.

(BMI), and smoking status. With regards to psychological variables, patients scored significant higher in the BDI II (F[1, 88]=38.61, P<0.001), the cognitive-affective symptoms subscale of the BDI II (F[1, 88]=40.14, P<0.001), the SOMS-7 (F[1, 88]=24.02, P<0.001), and the SOMS-2 (F[1, 83]=92.9, P<0.001). In terms of cytokines, patients had significantly higher concentrations of TNF-alpha (F[1, 87]=0.16, P=0.045). No group difference was found for IL-6. There were no significant interaction effects between group, sex, and time (P>0.05).

To test potential cross-sectional relationships between psychological variables and cytokines at baseline, bivariate correlations were performed. IL-6 and TNF-alpha are not significantly associated with BDI II (r=0.24, P=0.15; r=–0.7, P=0.7, respectively), the cognitive-affective symptoms subscale of the BDI II (r=0.11, P=0.52; r=–0.51, P=0.76, respectively), the SOMS-7 (r=0.18, P=0.28; r=–0.001, P=0.97, respectively), or the SOMS-2 (r=0.12, P=0.25; r=0.5, P=0.77, respectively).

For patients with major depression, a number of hierarchical regression analyses were conducted to examine if depressive and somatic symptoms (step 2) predict proinflammatory cytokines 4 weeks later after controlling for cytokine levels at baseline (step 1). The results for step 1 indicated that baseline levels of TNF-alpha (T1) were significantly related to TNF-alpha levels 4 weeks later (T2) (β=0.83, R^2=0.688, P<0.001). Regarding changes in TNF-alpha, neither total depressive symptoms (β=0.14, ΔR^2=0.019, P=0.147), cognitive-depressive symptoms (β=0.15, ΔR^2=0.021, P=0.124), somatoform symptoms during the last 7 days (P=0.557, ΔR^2=0.003, β=0.06), nor somatoform symptoms during the last 2 years (P=0.147, ΔR^2=0.021, β=0.14) were of significant predictive value.

Similar results were found for IL-6: the baseline levels of IL-6 (T1) were significantly related to IL-6 levels 4 weeks later (T2) (β=0.55, R^2=0.304, P<0.001). Like TNF-alpha, changes in IL-6 were not predicted neither from total depressive symptoms (β=0.04, ΔR^2=0.001, P=0.793), cognitive-depressive symptoms (β=–0.07, ΔR^2=0.005, P=0.626), somatoform symptoms during the last 7 days (β=–0.04, ΔR^2=0.002, P=0.772), nor somatoform symptoms during the last 2 years (β=0.08, ΔR^2=0.006, P=0.581).

Additionally, a number of moderation analyses were conducted to examine whether there were significant interactions between sex and symptom dimension in the prediction of changes in cytokines. Centered symptom scores and sex (dummy coded) were entered at step 2 after accounting for baseline levels of cytokines at step 1. Interaction terms of

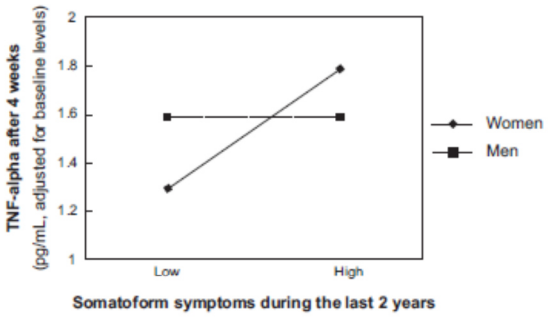

Figure 1 Sex as a moderator of the relationship between somatoform symptoms during the last 2 years (SOMS-2 scale) and an increase in TNF-alpha over 4 weeks.
Note: Somatoform symptoms during the last 2 years predict future levels of TNF-alpha in women but not in men (adjusted for baseline levels of TNF-alpha).
Abbreviations: TNF-alpha, tumor necrosis factor-alpha; SOMS-2, Screening for Somatoform Symptoms Scale-2.

centered symptom scores and sex were entered at step 3. Results indicated that interaction terms did not significantly explain variance (P>0.1) with one exception: SOMS-2 × sex interaction terms accounted for significant increments of variance in changes of TNF-alpha (β=–0.40, ΔR^2=0.046, P=0.027) beyond what was accounted for by sex (β=0.05; P=0.593) and SOMS-2 scores (β=0.14; P=0.167) at step 2 (ΔR^2=0.024; P=0.307). Figure 1 illustrates this significant interaction. Follow-up sex-stratified regression analyses indicated that higher somatoform symptoms during the last 2 years significantly predict an increase in TNF-alpha in women with major depression (β=0.31, ΔR^2=0.095, P=0.019), but not in men (β=–0.01, ΔR^2<0.001, P=0.930).

The calculation of ICC in the patient group showed a high ICC of 0.82 for TNF-alpha, which suggests strong stability of TNF-alpha over 1 month. Consistent with these findings, there was a significant correlation for TNF-alpha between T1 and T2 (r=0.83). The ICC for IL-6 was moderate (0.50) and similarly, there was a fair correlation between the two points of measurement (r=0.55). In the healthy control group, the ICC for TNF-alpha (0.55) was moderate as well (r=0.71), whereas the stability of IL-6 over 1 month was fair (ICC =0.43; r=0.43) (see Table 2). Calculations of ICC carried out separated by sex showed essentially equivalent results (data not shown).

Discussion

In the present study, we investigated whether changes in IL-6 and TNF-alpha over 4 weeks can be predicted by measures of cognitive-affective and somatic symptoms in patients with major depression. As a main result, we found that higher somatoform symptoms during the last 2 years significantly predict an increase in TNF-alpha in women

Table 2 Stability of cytokines indicated by ICC and correlation of inflammatory markers between baseline and 4 weeks follow-up

Baseline and 4 weeks follow-up		
	Pearson correlation	**ICC (95% CI)**
MD		
TNF-alpha (pg/mL)	0.825*	0.82 (0.69–0.90)
IL-6 (pg/mL)	0.504*	0.50 (0.22–0.71)
HC		
TNF-alpha (pg/mL)	0.553*	0.55 (0.30–0.72)
IL-6 (pg/mL)	0.432*	0.43 (0.16–0.64)

Note: *$P<0.01$ (two-tailed).
Abbreviations: CI, confidence interval; HC, healthy controls; ICC, intraclass correlation coefficients; IL-6, interleukin-6; MD, major depression; TNF-alpha, tumor necrosis factor-alpha.

with major depression but not in men. While TNF-alpha was significantly higher in patients with major depression, no group differences were observed for IL-6. Exploratory analyses indicated a high stability of TNF-alpha over 4 weeks in patients with major depression and a moderate stability in healthy controls. IL-6 was less stable in both groups.

Former research in healthy populations has shown that elevated cytokines are risk markers for coronary heart diseases.[28,29] Our finding that higher somatoform symptoms over the last 2 years significantly predicts an increase in TNF-alpha in depressive women is in line with previous results that link somatic symptoms with inflammatory markers and poor cardiovascular outcomes.[5,30] In women with suspected myocardial ischemia, somatic but not cognitive-affective depressive symptoms were associated with an increased risk of cardiovascular-related mortality and events.[6] Similarly, there are findings that in patients with CHF, only somatic depressive symptoms predict all-cause mortality in CHF.[7] Roest et al demonstrated in 2013 that changes in somatic depressive symptoms, but not in cognitive-affective symptoms of depression, were related to improved outcomes concerning event-free survival following acute myocardial infarction in cardiac patients.[31] A cross-sectional study found associations between somatic, but not cognitive symptom dimensions of depression and cardiovascular morbidity in the general population.[32] Furthermore, it was shown that only the somatic symptom dimension of depression was associated with increased levels of cytokines (IL-18- and IL-1-receptor antagonists). In patients with major depression, increased concentrations of sIL-2R were related to the severity of somatoform symptoms and somatic anxiety symptoms, but not to cognitive-affective depressive symptoms.[15] Considering the aforementioned links between inflammatory markers and cardiovascular health, our findings may support the idea that somatic symptoms can predict cytokine changes, which might be of potential relevance for cardiovascular disease.

Consistent with previous studies, our results confirm the important role of sex concerning the symptoms of depression and inflammation.[23,33] Prevalence rates of major depression are higher in women[34,35] and there is evidence that they develop more somatic symptoms than men with major depression.[36,37] Regarding inflammation, women show enhanced immunoreactivity and a higher risk for autoimmune diseases compared to men.[38] In 2004, Lekander et al showed that poorer subjective health was associated with higher levels of IL-1 and TNF-alpha in women but not in men.[39] In line with these observed sex differences, the present study demonstrated that for women, but not for men, somatoform symptoms of depression are meaningful predictors for future changes in proinflammatory markers. These markers in turn are predictors for the future course of depression, symptom severity, and potential cardiovascular diseases.[28,40,41] Further research as well as therapeutic and medical interventions to treat depression and prevent poor health should keep these findings in mind.

Our results regarding the stability of TNF-alpha and IL-6 show an acceptable stability of the cytokines over 4 weeks for both patients with major depression and controls. In particular, strong stability was observed for TNF-alpha. Compared to TNF-alpha, the ICC of IL-6 was less stable. These results are relevant for the interpretation of studies investigating issues concerning cytokines.

Although our study has strengths, such as the longitudinal design, some limitations have to be noted. The results should be interpreted with caution given the relatively small sample size. In addition, the larger number of women may bias our results. Finally, we measured TNF-alpha and IL-6 just over 1 month. To get more meaningful results, longer periods of measurement are needed.

In conclusion, our results provide further evidence for the importance of the differentiation between somatic and cognitive-affective symptoms in major depression. Somatic symptoms seem to be better predictors for changes in TNF-alpha than cognitive-affective symptoms in women with major depression.

Acknowledgments

We wish to thank all participants and our students Anina Burgbacher and Benedikt Bedenk for helping with the recruitment of participants.

This study was funded by a grant from the German Research Foundation (DFG) to Dr Rief (Ri 574/13). The

DFG had no further role in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report or in the decision to submit the paper for publication.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171–186.
2. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446–457.
3. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. *Brain Behav Immun*. 2009;23(7):936–944.
4. Halaris A. Inflammation, heart disease, and depression. *Curr Psychiatry Rep*. 2013;15(10):400.
5. Vaccarino V, Johnson BD, Sheps DS, et al. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study. *J Am Coll Cardiol*. 2007;50(21):2044–2050.
6. Linke SE, Rutledge T, Johnson BD, et al. Depressive symptom dimensions and cardiovascular prognosis among women with suspected myocardial ischemia: a report from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Arch Gen Psychiatry*. 2009;66(5):499–507.
7. Schiffer AA, Pelle AJ, Smith OR, Widdershoven JW, Hendriks EH, Pedersen SS. Somatic versus cognitive symptoms of depression as predictors of all-cause mortality and health status in chronic heart failure. *J Clin Psychiatry*. 2009;70(12):1667–1673.
8. Myint AM, Kim YK, Verkerk R, Scharpé S, Steinbusch H, Leonard B. Kynurenine pathway in major depression: evidence of impaired neuroprotection. *J Affect Disord*. 2007;98(1–2):143–151.
9. de Jonge P, Ormel J, van den Brink RH, et al. Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry*. 2006;163(1):138–144.
10. Smolderen K, Spertus J. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2009;2(4):328–337.
11. Bosch NM, Riese H, Dietrich A, Ormel J, Verhulst FC, Oldehinkel AJ. Preadolescents' somatic and cognitive-affective depressive symptoms are differentially related to cardiac autonomic function and cortisol: the TRAILS study. *Psychosom Med*. 2009;71(9):944–950.
12. de Jonge P, Mangano D, Whooley MA. Differential association of cognitive and somatic depressive symptoms with heart rate variability in patients with stable coronary heart disease: findings from the heart and soul study. *Psychosom Med*. 2007;69(8):735–739.
13. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry*. 1996;39(6):411–418.
14. Duivis HE, Vogelzangs N, Kupper N, de Jonge P, Penninx BWJH. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA). *Psychoneuroendocrinology*. 2013;38(9):1573–1585.
15. Euteneuer F, Schwarz MJ, Dannehl K, Hartung A, Westermann S, Rief W. Increased soluble interleukin-2 receptor levels are related to somatic but not to cognitive-affective features in major depression. *Brain Behav Immun*. 2012;26(8):1244–1248.
16. Kupper N, Widdershoven JW, Pedersen SS. Cognitive/affective and somatic/affective symptom dimensions of depression are associated with current and future inflammation in heart failure patients. *J Affect Disord*. 2012;136(3):567–576.
17. Shanahan JC, St Clair W. Tumor necrosis factor-α blockade: a novel therapy for rheumatic disease. *Clin Immunol*. 2002;103(3):231–242.
18. Coussens L, Werb Z. Inflammation and cancer. *Nature*. 2002;420(6917):860–867.
19. Cesari M, Penninx BWJH, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. *Circulation*. 2003;108(19):2317–2322.
20. Salanitro AH, Ritchie CS, Hovater M, et al. Inflammatory biomarkers as predictors of hospitalization and death in community-dwelling older adults. *Arch Gerontol Geriatr*. 2012;54(3):e387–e391.
21. Shanmugasegaram S, Russell KL, Kovacs AH, Stewart DE, Grace SL. Gender and sex differences in prevalence of major depression in coronary artery disease patients: a meta-analysis. *Maturitas*. 2012;73(4):305–311.
22. Steiner M. Serotonin, depression, and cardiovascular disease: sex-specific issues. *Acta physiol (Oxf)*. 2011;203(1):253–258.
23. Pennell LM, Galligan CL, Fish EN. Sex affects immunity. *J Autoimmun*. 2012;38(2–3):J282–J291.
24. Wittchen HU, Wunderlich U, Gruschitz S, Zaudig M. *Strukturiertes Klinisches Interview für DSM-IV, Achse I (SKID-I)* [*The structured clinical interview for DSM-IV, Axis-I, SCID-I*]; 1997. German.
25. Hautzinger M, Keller F, Kühner C. *Das Beck Depressions Inventar II*. Deutsche Bearbeitung und Handbuch zum BDI II. Frankfurt: Harcourt Test Services; 2006. German.
26. Rief W, Hiller W. *Screening für Somatoforme Störungen: SOMS* (2., vollständig überarb. und neu normierte Aufl.). Bern, Göttingen, Toronto, Seattle: Huber; 2003. German.
27. Fox J. *Regression Diagnostics: An Introduction*. Thousand Oaks, CA: Sage Publications; 1991.
28. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;1(8):1066–1067.
29. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*. 2000;101(15):1767–1772.
30. Shimbo D, Chaplin W, Crossman D, Haas D, Davidson KW. Role of depression and inflammation in incident coronary heart disease events. *Am J Cardiol*. 2005;96(7):1016–1021.
31. Roest AM, Carney RM, Freedland KE, Martens EJ, Denollet J, de Jonge P. Changes in cognitive versus somatic symptoms of depression and event-free survival following acute myocardial infarction in the Enhancing Recovery In Coronary Heart Disease (ENRICHD) study. *J Affect Disord*. 2013;149(1–3):335–341.
32. Michal M, Wiltink J, Kirschner Y, et al. Differential associations of depressive symptom dimensions with cardio-vascular disease in the community: results from the Gutenberg health study. *PLoS one*. 2013;8(8):e72014.
33. Oertelt-Prigione S. The influence of sex and gender on the immune response. *Autoimmun Rev*. 2012;11(6–7):A479–A485.
34. Delisle VC, Beck AT, Dobson KS, Dozois DJ, Thombs BD. Revisiting gender differences in somatic symptoms of depression: much ado about nothing? *PLoS one*. 2012;7(2):e32490.
35. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*. 2008;33(6):693–710.
36. Silverstein B. Gender differences in the prevalence of somatic versus pure depression: a replication. *Am J Psychiatry*. 2002;159(6):1051–1052.
37. Kroenke K, Spitzer RL. Gender differences in the reporting of physical and somatoform symptoms patient characteristics. *Psychosom Med*. 1998;60(2):150–539.

38. Cannon J, Pierre BS. Gender differences in host defense mechanisms. *J Psychiatr Res*. 1997;31(1):99–113.
39. Lekander M, Elofsson S, Neve IM, Hansson LO, Undén AL. Self-rated health is related to levels of circulating cytokines. *Psychosom Med*. 2004;66(4):559–563.
40. Lindqvist D, Janelidze S, Hagell P, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol Psychiatry*. 2009;66(3):287–292.
41. Gimeno D, Kivimaki M. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol Med*. 2009;39(3):413–423.

9.4. Vitae und Publikationen

(Die Vitae ist nicht Teil der Veröffentlichung).

9.5. Erklärung

Ich versichere, dass ich meine Dissertation

„*Major Depression - neuropsychologische und immunologische Aspekte eines heterogenen Störungsbildes*“

selbstständig ohne unerlaubte Hilfe angefertigt und mich dabei keiner anderen als der von mir ausdrücklich bezeichneten Quellen und Hilfen bedient habe.

Die Dissertation wurde in der jetzigen oder einer ähnlichen Form noch bei keiner anderen Hochschule eingereicht und hat noch keinen sonstigen Prüfungszwecken gedient.

Marburg an der Lahn, März 2017 Katharina Dannehl